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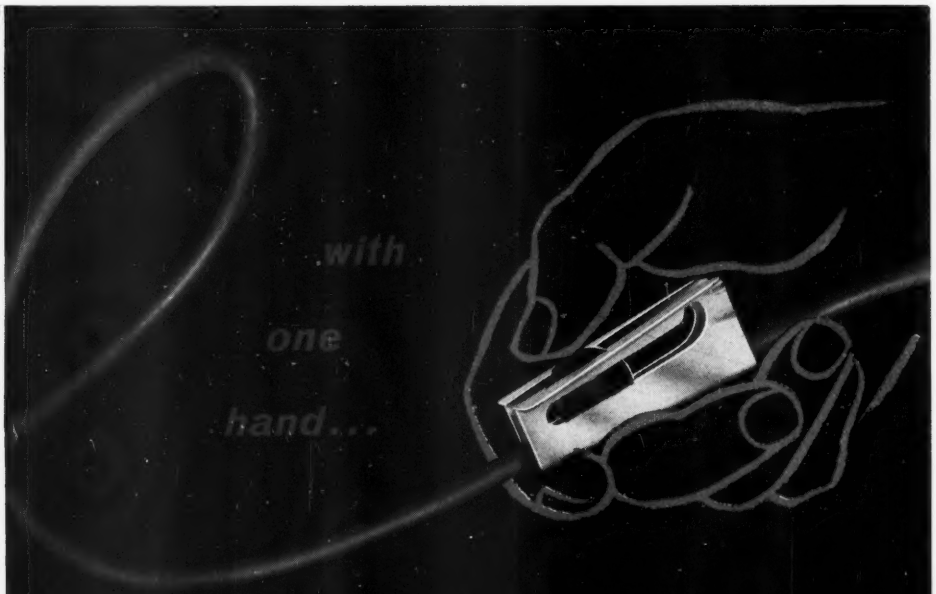

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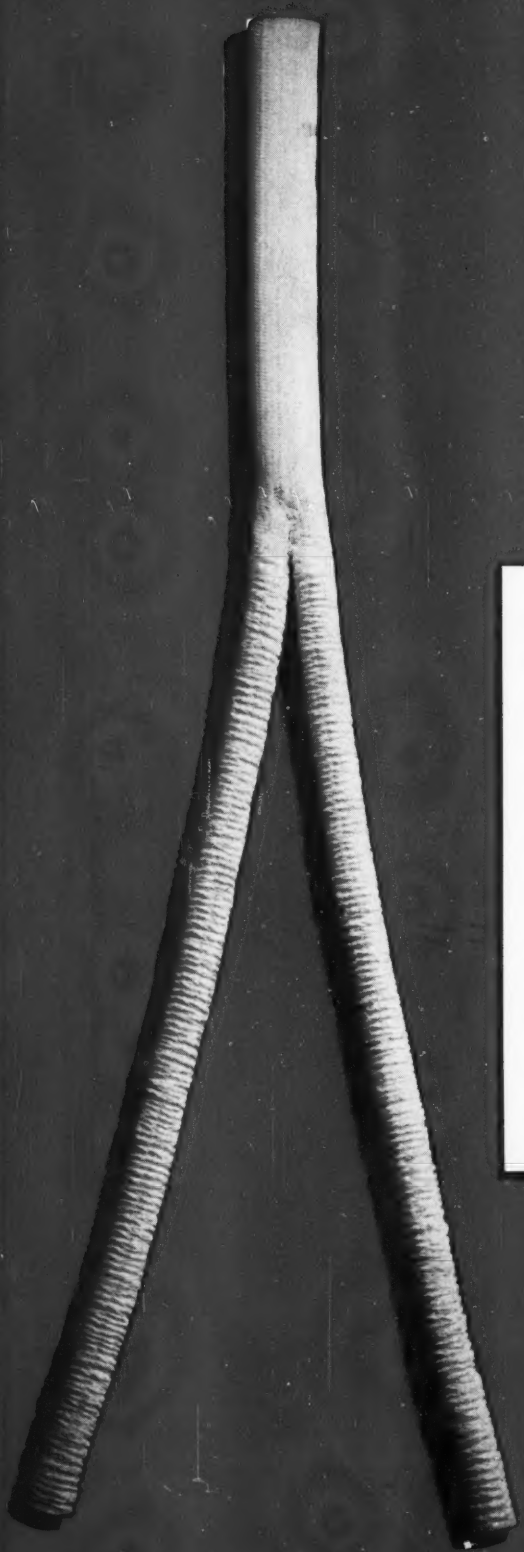

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Gynecology & Obstetrics VOLUME 103
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FLASH BURNS FROM ATOMIC WEAPONS

I. Observations on Flashburning of Human Subjects in the Laboratory Using Infrared and Predominantly White Light Sources

W. J. H. BUTTERFIELD, O.B.E., M.D., E. R. DRAKE SEAGER, B.Sc., A. Inst. P., J. R. B. DIXEY, M.B., B.Ch., and E. E. E. TREADWELL, London, England

THE DETONATION of an atomic weapon in air releases a large amount of energy, about one-third of which is emitted as thermal radiation. This latter constitutes the heat flash. The burns which result from exposure of the skin to this thermal energy, as reported by Solandt, are called flash burns. The present communication describes laboratory experiments designed to simulate and study such flash burns.

When the present investigations were begun in 1948, the problems demanding attention were the range and clinical aspects of flashburning injury, and the healing time of uninfected flash burns. These questions are especially pertinent to the casualties from air-burst explosions against unwarned communities. The answers to them hold important implications for the strategist, the doctor and hospital administrator, and for the citizen, as has been pointed out by Pearse and Payne and by Butterfield. The problems could not be resolved from the explosions in Japan, where the thermal energy released was not measured. Again, although the thermal energy emitted by atomic explosions was measured at subsequent tests, and animals were exposed by Pearse and Kingsley at American trials, the range, symptoms, and healing time of human flash burns cannot be deduced accurately from these data. It therefore seemed important to induce flash burns in man, using measured quantities of radiant energy, for comparison with the radiant energy from atomic explosions.

Preliminary trials in the laboratory revealed the difficulties of reproducing the spectral distribution, intensity, and duration of the heat flash from an atomic weapon. They also suggested that the threshold doses of radiant energy for some physiologic effects, especially pain, were altered by changing the size of the skin surface exposed. Since the threshold dose is

From Guy's Hospital, London, and the Army Operational Research Group, Byfleet, Surrey, England.
Dr. Butterfield, working on behalf of the Medical Research Council.

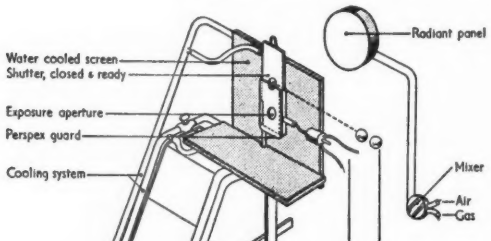

FIG. 1. Diagram of apparatus used for infrared flashburning.

important in assessing ranges of effects, we were brought to investigate this phenomenon first. This demanded methods of irradiating up to 20 square centimeters of skin. It was not feasible to develop a suitably large white light source, with a spectrum resembling that of the heat flash from an atomic weapon. But using a gas-fired infrared radiation panel we could obtain steady, even, and intense irradiation of such areas of skin and so examine the effect of area upon thresholds. Thereafter, we were in a position to proceed to flashburning with a convenient white light source: this was necessary as infrared radiation represents only 30 to 40 per cent of the heat flash from airburst atomic weapons.

INFRARED FLASH BURNS

Apparatus. The source of infrared energy was a vertical gas-fired radiant panel (Fig. 1). During experiments, its surface temperature was maintained at 1,000 degrees C., as measured by a disappearing filament pyrometer. The spectral emission of such a source, described by Roberts and Long in 1948, is shown in Figure 2 together with curves for skin transmission derived from the findings of Hardy and Muschenheim and of Buttner. The skin was exposed to this energy through an aperture in a sliding shutter. Behind the shutter was a stationary perspex guard, against which the subjects held their arms. The shutter was open automatically for 1 second, a time period chosen as corresponding roughly to the duration of the flash from an atomic weapon. To change the area of skin irradiated, the aperture was altered by inserting stops 5, 3, and 1 centimeter in diameter. A large water-cooled screen was arranged to shield the subject. Even irradiation over the aperture was checked frequently with heat sensitive paper. The dose of radiant energy could be increased by moving the apparatus toward the radiant panel. Each dose of radiant energy falling on the skin was measured with a specially designed thermopile, calibrated by the National Physical Laboratory.

Procedure. Eight healthy males, aged 20 to 32 years, and varying in complexions from fair to dark, volunteered for the experiments. Circular areas 5, 3, and 1 centimeter in diameter, of the unshaven skin of the extensor aspect of the forearms were exposed to the source. The experiments extended over 5 days, the distance from the radiant panel being gradually decreased until blister burns were inflicted on the last day. A fresh site was carefully chosen for each exposure; Gregg has shown how important this is to avoid irradiation of skin still warm from a previous exposure. The skin temperature in our cases ranged from 28 to 33 degrees C. The site chosen was then carefully aligned behind the shutter and the exposure made. The order of exposure of subjects for each dose was randomized.

The subject reported his sensations immediately, and the area exposed was observed continuously for several minutes, and then at intervals. All blister burns were cleaned with cetavlon,[1] dressed with penicillin cream (400 units per ml.), and covered with an occlusive dressing. Bacteriologic swabs were taken whenever these dressings were changed to examine the burns (every 1 to 2 days). The criteria for healing were absence of soreness to touch or, in the case of blister

[1]Acetyl-tri-methyl ammonium bromide (cetrimide).

burns, firm healing of the epithelium over the burn.

Results. The results obtained using the 3 centimeter diameter aperture may be summarized as follows: With low doses, subjects reported a local tingling sensation at the end of exposure. With higher doses, pain was felt. It occurred earlier in the exposure as the dose increased. It had a stinging quality and was associated with a strong inclination to withdraw the arm (which was always successfully resisted). Pain occurred in all subjects when the doses exceeded 0.76 calorie per square centimeter given in 1 second. The sensation subsided immediately at the end of irradiation.

Minimal first degree burns followed doses of 0.94 to 1.23 calories per square centimeter in 1 second. These showed erythema, which appeared in the irradiated area 30 seconds after burning and lasted for 2 to 10 minutes. Higher doses caused erythema lasting several days.

Blister burns resulted when doses exceeded 1.8 to 2.35 calories per square centimeter given in 1 second. These were associated with intense pain limited to the period of exposure. Thirty seconds after exposure, erythema appeared, associated with continuous, dull burning pain which subsided after several hours. A flare appeared beyond the irradiated area, and edema localized to the irradiated area became visible by the end of an hour. Blisters formed in 4 to 24 hours. The burns oozed and were sore for 7 to 10 days. With 1 exception, the blister burns were kept free from infection and healed in 12 to 24 days. Later, the skin at and around the burned sites showed a variety of pigmentation and depigmentation reactions, some of which could be discerned 5 years later.

Table I shows the individual results for the various doses given.

The median effective doses required to produce these symptoms and signs in the 8 male subjects have been derived by interpolation from Table I and are shown in Figure 3. Comparison of these findings with

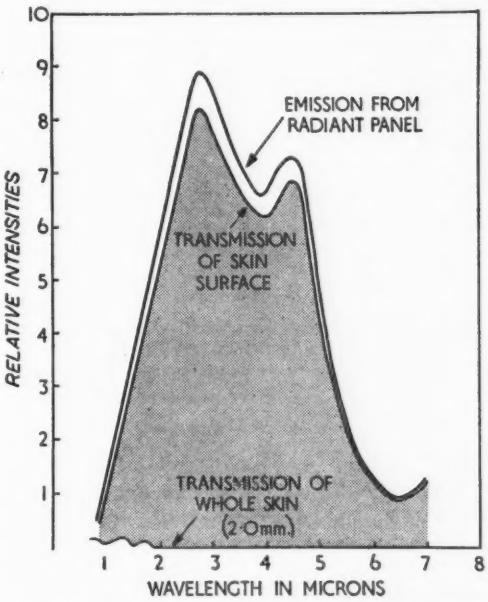

FIG. 2. Curves showing: (1) spectral distribution of radiation falling on skin from infrared source; (2) transmission of skin surface; (3) penetration beyond 2.0 millimeter depth into skin. The area between top and middle curves represents skin reflection. The shaded area represents absorption in the skin, from surface to 2.0 millimeter depth.

those from selected doses using 5 and 1 centimeter diameter apertures shows that the size of the aperture influences the threshold dose for pain and first degree burning. Thus, 0.70 calorie per square centimeter induced pain in all subjects when a 5 centimeter diameter aperture was used, but in only 1 subject out of 8 when a 3 centimeter diameter aperture was used, and no sensation at all in any subject when a 1 centimeter diameter aperture was used. Again, a dose of 0.94 calorie per square centimeter gave transient reddening of the skin in 5 subjects out of 8 when a 3 centimeter diameter aperture was used, but in only 1 subject when a 1 centimeter diameter aperture was substituted. These changes in threshold will be reported separately. On the other hand changing the area of skin exposed, even by a factor of 25, had little effect on the threshold for blister burning. For, whether

TABLE I.—RESULTS OF EXPOSING CIRCULAR AREAS, 3 CENTIMETERS IN DIAMETER, OF THE EXTENSOR ASPECTS OF THE FOREARM TO VARIOUS DOSES OF INFRARED RADIATION DELIVERED IN 1 SECOND

	Doses of infrared radiation, calories per sq. cm.											
Subject	*.70*	*.76*	*.81*	*.87*	*.94*	*1.02*	*1.11*	*1.23*	*1.39*	*1.57*	*1.80*	*2.35*
1.....	T	p	P	P	e	e	e	e	E	E	E	B
2.....	T	p	p	P	e	e	e	e	e	E	E	B
3.....	p	p	P	P	e	e	e	e	E	E	E	B
4.....	—	t	p	P	P	P	e	e	E	E	B	B
5.....	T	T	p	P	e	e	e	e	E	E	E	B
6.....	t	p	P	P	P	e	e	e	e	E	E	B
7.....	t	p	P	e	e	e	e	e	E	b	B	B
8.....	t	p	P	P	P	e	e	e	e	E	E	B

Key: —= No sensation.
t= Sensation described as tingling.
T= Sensation described as pronounced tingling but not pain.
p= Sensation described as painful.
P= Sensation described as intense pain.
e= Transient erythema, lasting a few minutes.
E= Long lasting erythema, a first degree burn.
b= Minimal blistering.
B= Blister burning, shallow partial skin loss.

a 5 or 3 centimeter diameter aperture was used, 2.35 calories per square centimeter caused blister burns in all subjects. The same intensity produced blister burns in 6 of the 8 subjects when the 1 centimeter diameter aperture was employed. Furthermore, all 22 blister burns healed in 12 to 14 days. Since healing takes place from below in such shallow blister burns, this finding also indicates that the injuries were substantially similar irrespective of the area of skin exposed.

FLASH BURNS FROM PREDOMINANTLY WHITE LIGHT

Apparatus and procedure. The most relevant result of the infrared studies was the inconspicuous effect of the dimensions of skin exposed upon the threshold dose for blister burning. Consequently, a 1 centimeter diameter aperture was used for white light flash burns as an acceptable basis for conservative predictions about larger burns. This method obviated the need for a white light source sufficiently powerful to produce steady, even, and suitably intense irradiation over larger areas. Preliminary trials with a 20 inch searchlight showed that its arc was not stable. Eventually it was found that a cinema projector with an 8 millimeter carbon arc in an elipsoidal reflector (Fig. 4) provided a satisfactory source. The spectral distribution of the reflected beam derived from Finkelnburg is shown in Figure 5 together with curves for skin transmission compiled from Buttner, Pearson and Gair, Bachem and Reid, and Kuppenheim and Heer.

During experiments the arc was monitored visually and electrically. The evenness of irradiation over the target area in the concentrated beam was checked frequently with heat-sensitive paper. The intensity of the radiant energy was measured by the rise in temperature over a fixed period of time of a well insulated copper block calorimeter.

The exposure of a subject's skin was again controlled by means of a mechanically operated shutter. The total dose was altered by changing the duration of the exposure. Although this might appear to invalidate direct comparisons between doses, Perkins and associates have shown that such variations in exposure time have little effect on burning thresholds in pigs.

The extensor aspects of the forearms of 7 male subjects (ranging in complexion from fair to dark) were used; the procedure was the same as that described for the infrared flash burns.

Results. The doses given ranged from 2.0 calories per square centimeter in 0.17 second to 5.25 calories per square centimeter in 0.45 second. All exposures were associated with intense stinging pain at the site of the burn. A dose of 2.0 calories per square centimeter caused transient erythema or first degree flash burns in all but 1 subject, in whom a blister burn resulted. The stinging pain subsided immediately the exposure was over and the burned skin appeared normal. After 30 to 60 seconds erythema appeared in a well circumscribed area coinciding with the site exposed. This condition was associated with a dull pain which subsided after a few hours. The erythema, with soreness to touch, lasted a variable time, from a few hours to a day or two.

A dose of 3.5 calories per square centimeter delivered in 0.30 second inflicted shallow second degree burns (shallow partial skin

loss) or deeper burns in all subjects. These had courses similar to that described for first degree burns, except that subcutaneous edema and blisters appeared in that order over a period of 1 to 30 hours.

A dose of 4.8 calories per square centimeter given in 0.45 second usually produced deep second degree burns (deep partial skin loss). There was intense pain during exposure. Immediately afterward, the irradiated area was blanched, a finding in marked contrast to the effects of lower doses. One minute after burning the blanching gave way to erythema and dull pain was felt. There was loss of sensation to pinprick which is now recognized to occur in deep partial skin loss burns. Half an hour after burning local circumscribed edema was present, and small surface blisters appeared during the next few hours.

A dose of 5.25 calories per square centimeter delivered in 0.45 second to 1 subject caused third degree burning injury (whole skin loss). The skin was blanched immediately after exposure; charring was not seen. Over the still pale burned area there was loss of sensation to pinprick which Bull and Lennard-Jones have described. Edema appeared at the burned site after a few hours, and marginal blisters were apparent after 24 hours. Over the next few days the injury remained sore and by the fifth day the margin of the previously white region showed a pinkish hue. The central zone remained white. Healing occurred slowly from the circumference, with sloughing of the central area. The scar of this burn was discernible 5 years later; hair follicles survived just within the circumference.

The incidence of clinical effects differed at the various doses. To derive the approximate median threshold doses for white light flash burns, the result of the series have been interpolated as was done with the infrared results (Fig. 6). Our data are inadequate to identify any effect on the severity of the burn from skin texture or color.

None of the white light flash burns became infected. The course of all burns was followed until soreness to touch disappeared and the skin healed. Soreness tended to outlast anatomic repair with shallow burns, but not with deeper burns. In Figure 7 the mean healing times for each group of burns are plotted against the doses of radiant energy delivered per square centimeter, together with a curve fitted to these data by the method of least squares. The equation for this curve is:

$$t = 0.92q^2 + 1.26q - 4.26$$

where t = healing time in days and q = dose in calories per square centimeter.

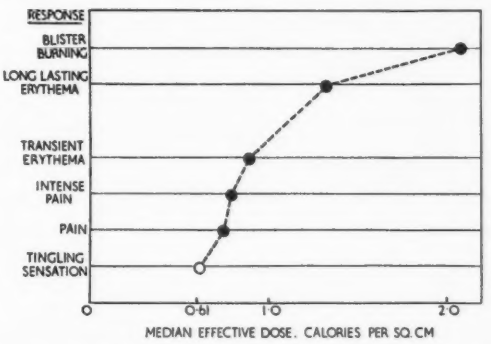

FIG. 3. Median effective doses of infrared radiation for various effects. Source temperature 1,000 degrees C.; male subjects; circular burns, 3 centimeter diameter; results interpolated from Table I.

THRESHOLDS FOR BURNING INJURY

We have been unable to trace any reports of experimental human burns from infrared energy falling on the skin in 1 second or less. However, in their studies of cutaneous pain, Hardy, Wolff, and Goodell produced burns in the skin of the volar aspects of forearms. Although they used a white light filament lamp, their experiments are comparable to our infrared studies because they blackened the skin surface with Indian ink. Thus skin reflection, which dissipates a large proportion of white light, but not infrared radiation, was reduced to a minimum. They exposed 3.5 square centimeters of skin, that is, about half the area we exposed using our 3 centimeter diameter aperture. The duration of their exposures, 3 seconds, was longer than ours. The threshold doses they reported are

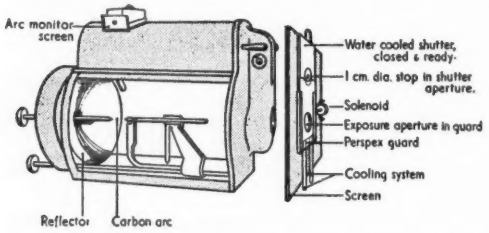

FIG. 4. Diagram of apparatus for predominantly white light flashburning.

0.69 calories per square centimeter for pain, 1.2 to 1.44 calories per square centimeter for erythema and 1.5 to 2.1 calories per square centimeter for blistering. Their thresholds are slightly lower than those we observed. The differences could be accounted for by the differences in experimental techniques, skin blackening, and timing.

The median effective doses for shallow blister burns from predominantly white light were higher than with infrared radiation, 3.0 compared to 2.1 calories per square centimeter. This fact can be explained partly by the high proportion of white light reflected by the skin, as demonstrated by the curves shown in Figures 2 and 5. The agreement between the two sets of results, using infrared radiation and predominantly white light, is remarkably close if we consider the energies absorbed in the superficial layers of the skin as follows. By integrating the curves shown in Figures 2 and 5, 92 per cent of the incident radiation from the infrared source would be absorbed in the skin from the surface down to a depth of 2 millimeters in contrast to 53 per cent of the incident radiation from the carbon arc source. Thus, with infrared radiation, of the 2.1 calories per square centimeter incident on the skin surface which caused blister burns, 1.9 calories would be absorbed per square centimeter down to a depth of 2 millimeters. This figure, 1.9, compares closely to 1.65 calories absorbed per square centimeter down to the same depth out of 3.0 calories per square centimeter incident on the skin from the carbon arc source. We conclude that the two sets of results for shallow blister burns, from predominantly white light and infrared radiation, confirm each other, and that the injury is probably related to the amount of energy dissipated in the superficial layers of the skin, rather than its spectral qualities.

Agreement is close between the thresholds we observed for flash burns from predominantly white light (Fig. 6), and those reported recently by Perkins and Evans and their associates whose source, methods of calibration, and exposure times were similar to ours.

It is noteworthy, as an example of the differences between species or age, that Morton and his co-workers found 4.5 calories per square centimeter caused "coagulation of the skin," presumably third degree burns, in young Chester pigs, whereas 4.8 calories per square centimeter produced blister burns, without "coagulation of the skin," in our experience with human skin.

CLINICAL ASPECTS OF THE PRESENT OBSERVATIONS

Pain and erythema. In the infrared studies, the threshold dose for pain and erythema varied according to the aperture size. These findings with pain thresholds conflict with those reported by Hardy, Wolff, and Goodell who found the threshold dose to be independent of the area exposed. To explain their results we suggest that their apparatus did not achieve even irradiation over larger areas and that pain in their observations was always due to the focussed image of the filament of the lamp used as radiation source. We ensured even irradiation in all our studies and our results reopen the possibility of summation of painful stimuli, which those investigators deny.

Erythema and shallow blister burns. We were interested by the delay between exposure of the skin to radiant energy and the appearance of local erythema, edema, and blistering. One explanation of the slow progression of changes is that they are dependent upon a chemical mediator, or mediators, released in the most superficial layers of the skin, where the radiant energy was mainly ab-

sorbed and where it presumably had its greatest immediate effect. If this were so, the delayed appearance of local changes could be attributed to the time taken for such a substance or substances to diffuse down to the blood vessels. We do not know the nature of this substance or substances. Harkins listed 20 substances which have been suggested as toxic products of thermal injury but we were more interested in histamine which has been studied in relation to ultraviolet light burns by Lewis and Zotterman. More recently, Emmelin and Feldberg have shown that a mixture of histamine and acetylcholine pricked into the skin induces a burning sensation. Armstrong, Dry, Keele, and Markham report that 5-hydroxytryptamine applied to the base of a cantharides blister induces a painful sensation 15 to 45 seconds after application; a similar response followed the application of fluid aspirated from a blister burn. We have pricked histamine, acetylcholine and 5-hydroxytryptamine alone and in combination into the skin of the forearm in various concentrations. We could not induce a pattern of reaction resembling the sensations, timing, and localized nature of the erythema and edema after flashburning. The only common feature of these observations and flash burns was the flaring induced by pricking in histamine solutions. This fact suggests that released substance plays a role in local changes after flashburning. Although edema in flash burns was discrete to the irradiated area whereas wheals spread from the site of pricking strong histamine solutions into the skin, discrete wheals have been observed by McArdle when small doses are introduced into the skin by iontophoresis.

If the local lesions in blister burns from radiant heat are due to chemical agents, we consider that these agents are released or activated by local heating, rather than by bond-splitting induced by the incident energy. This conclusion is based on the fact that the slow development of clinical changes was seen with infrared radiation as well as with carbon arc radiation. Infrared photons

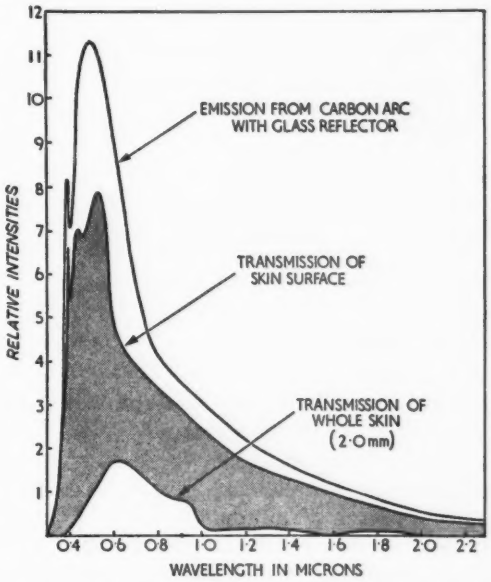
RELATIVE INTENSITIES
EMISSION FROM CARBON ARC WITH GLASS REFLECTOR
TRANSMISSION OF SKIN SURFACE
TRANSMISSION OF WHOLE SKIN (2·0mm)
WAVELENGTH IN MICRONS
0·4 0·6 0·8 1·0 1·2 1·4 1·6 1·8 2·0 2·2

FIG. 5. Curves showing: (1) spectral distribution of radiation falling on skin from predominantly white light apparatus; (2) transmission of skin surface; (3) penetration beyond 2.0 millimeter depth into skin. The area between top and middle curves represents skin reflection. The shaded area represents absorption in the skin, from surface to 2.0 millimeter depth.

have low energies, of 1 electron volt or less. These energy levels are generally regarded as being too low to dissociate molecular bonds.

Deep blister burns and third degree burns. Deep blister and third degree flash burns from predominantly white light were associated with immediate and intense blanching at the irradiated site. A dose of 4.8 calories per square centimeter caused blanching, which was not seen with the lower doses. The blanching lasted about a minute and then gave way to erythema, edema, and blistering. The vasospasm underlying the blanching could be due to direct stimulation from the higher doses of incident energy. A proportion of white light falling on the skin penetrates deeper than 2 millimeters, which is deeper than the skin capillaries. It is possible that more prolonged vasospasm was induced by 5.25 calories per square centimeter; this may have played a role in pro-

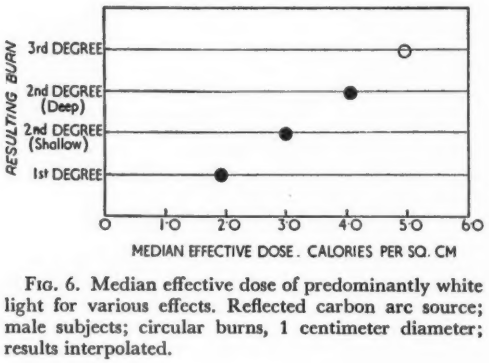

FIG. 6. Median effective dose of predominantly white light for various effects. Reflected carbon arc source; male subjects; circular burns, 1 centimeter diameter; results interpolated.

ducing the skin necrosis of third degree burning which that dose caused.

Healing times. We have been unable to trace any investigations or analyses of the healing times of human flash burns from graded doses of radiant energy; most experimental studies of flashburning so far reported from the United States have been performed on pigs or dogs. In young Chester white pigs, burns caused by 5.5 calories per square centimeter healed in some 14 days. This is considerably faster than obtained with human burns from the same or lower doses. One reason for the differences may be the criteria of healing adopted. In the present series of human burns, healing was taken as absence of soreness to touch and epithelization of the burned site. The former criterion seemed important because flashburning would be likely to affect the hands, and soreness there would interfere with occupational activities.

It will be seen from the formula relating healing times and doses of predominantly white light that the healing time for 1 centimeter diameter burns becomes finite when the dose exceeds 1.5 calories per square centimeter. Although this dose was not actually used in the carbon arc observations, there are good reasons for believing it to be the correct figure. If 1.6 calories per square centimeter of predominantly white light were given, 0.85 calorie per square centimeter would be absorbed down to 2 millimeters; 0.92 calorie per square centimeter of infrared radiation from the furnace would be required to present the same dose to the same depth. This last figure is in close agreement with 0.94 calorie per square centimeter, which dose is known to have caused erythema, i.e. a finite healing time, in the infrared flash burns using a 1 centimeter diameter aperture. When it is recalled that increasing the aperture size diminished the threshold for erythema in the infrared burns, it seems reasonable to assume that flash burns caused by 2.0 calories per square centimeter of predominantly white light over large skin areas, such as a hand or face, would cause some disability.

CONCLUSIONS

The information from the present observations may be used to infer the clinical course of uninfected flash burns after the explosion of an atomic weapon. The dose levels of heat with which we have been here concerned, up to 5.25 calories per square centimeter, would not cause burns through clothing nor flame burns through the ignition of clothing. Thus these flash burns would involve only uncovered skin exposed directly to the heat flash, that is, face, neck, hands, wrists, and forearms in men, and also the legs in the case of women and children. Through knowledge of the threshold thermal doses required to produce them, the range of various degrees of flashburning can be deduced from the thermal doses received from air-burst atomic weapons, as set out in *The Effects of Atomic Weapons* (1950). However, we believe that appraisals based on the present data, derived from observations on young male adults, would give conservative estimates of casualties among the general population: other unpublished investigations have shown that, although the threshold for blister flashburning on the extensor aspect of the fingers is much the same as for the forearms, the threshold for thermal effects appears to be lower on the face than on the forearms and lower in females than in males. These points must be borne in mind in following the ensuing account of the course to be

expected after flashburning from atomic weapons.

The sudden impact of a sufficient dose of radiant heat from an atomic explosion falling on the skin causes an immediate intense brief stinging pain localized in the exposed area. If the heat dose is less than 1.5 calories per square centimeter, no signs of burning follow. As the dose approaches 2.0 calories per square centimeter, the threshold for significant first degree burns, the stinging sensation is followed, after about 30 seconds, by a shorter or longer erythema of the exposed area and by the other signs listed in the following.

1. *In first degree flash burns* (dose about 2.0 calories per sq. cm.) the erythema increases in intensity for about an hour. It is by then surrounded by a flare, extending for about 2 centimeters beyond the edge of the burns and is associated with a dull burning pain. The flare persists for several hours, the burning pain for about 24 hours. Thereafter the burned area remains reddened and sore to touch for up to 8 days. Desquamation of fine flakes of epithelium follows and during the next few weeks the burned skin becomes pigmented. Such burns do not disable but involvement of the hands would impair efficiency for manual tasks.

2. *In second degree flash burns* (dose about 3.0 calories per sq. cm.) the phenomena are at first the same as those for slighter burns except that the skin is discolored by singed hairs and the dull burning pain is more intense. By 1 hour, the burned area shows circumscribed edema and after 2 to 30 hours, depending in part upon environmental conditions, becomes blistered. The blisters ache and ooze serum for 3 to 4 days, after which the burn is covered with a thin eschar of dried serum. This separates by the sixth to eighth day, when dilated blood vessels filled with cyanotic blood would be visible in the base of the area ulcerated by the burn. In such burns healing apparently takes place from skin elements surviving deep in hair follicles and sweat glands, since epithelization occurs evenly over the burned area and not from edges. These burns are tender to pressure and easily injured through the thin epithelial covering for 8 to 14 days. It is noteworthy that such shallow blister flash burns can easily become infected; this fact was observed in 1 instance among experimental flash burns inflicted in the laboratory, despite an occlusive dressing which was applied to it with full facilities for careful and unhurried treatment. This infected burn took 6 weeks to heal.

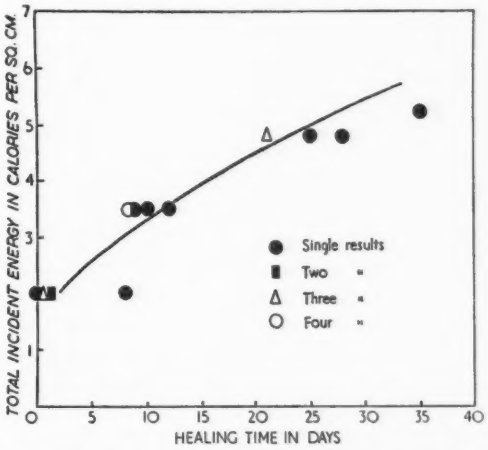

FIG. 7. Healing time of flashburns from predominantly white light Curve showing relationship between healing time and dose.

Incapacitation would not be complete with uninfected shallow blister flash burns, unless palpebral edema and oozing interfered with vision. Edema of the lips might necessitate a liquid diet for a few days. Manual dexterity would be severely restricted by such burns of the hand. During the first 24 to 48 hours, the burning pain of such flash burns over extensive areas would, we believe, be distracting; it was probably this sensation which led the Japanese casualties to apply compresses to their burns in a search for relief. Incapacitation would be more extensive and prolonged if such blister flash burns were permitted to become infected.

Nearer the explosion, closing to the range of third degree flash burns, the radiant en-

ergy falling on the skin would induce local vasoconstriction and cause blanching. The symptoms during exposure, intense brief stinging pain, would be the same as described before. The blanching would give way to erythema after 1 minute. Such burns are insensitive to pinprick in the early stages. The subsequent course of such burns would be similar to that of shallow blister flash burns, except that healing, in the absence of infection, would not be secure until 3 to 4 weeks. Incapacitation would be correspondingly prolonged. Pigmentation changes have been observed in and around experimental second degree flash burns for many months after healing.

3. *In third degree flash burns* (dose about 5.25 calories per sq. cm. or more) the brief intense pain is also followed by blanching. The margins of the burns pucker. The burns are insensitive to pinprick. Edema is visible below the blanched area 1 hour after burning, and lasts about 2 days. A bluish tinge, suggesting sluggish flow or stagnant blood, may be observed in the blanched areas several hours after injury. By 24 to 36 hours a narrow zone, 1 to 2 millimeters wide, of blister burns becomes discernible around the edges. The burned areas remain sore for 7 to 10 days, and tender to pressure until healed. The burned skin in the blanched area gradually separates from the surrounding skin during the third week and sloughs away with a central core by the middle of the fourth week. Epithelization takes place from the edges of small experimental burns before granulations are established at the base of the resulting ulcer. The epithelium is sufficiently robust for healing to be regarded as satisfactory by the end of the fifth week. It is to be expected that if such burns occurred over areas wider than 2 centimeters, sloughing would be followed by the formation of granulation tissue. In this event, plastic surgical treatment would be required to prevent scar formation, to effect satisfactory healing, and to restore adequate function. The time for healing in such casualties after an atomic attack would, therefore, depend upon the surgical resources available to treat such injuries.

Incapacitation would be greater than with the injuries described previously. Although perhaps not so painful as shallower injuries, the tightness of the destroyed skin overlying edematous tissues and the symptoms from marginal blister and first degree burns would cause discomfort in the early stages. Once sloughing had taken place, incapacitation would be due to the delicacy of the epithelium growing from the edges of the burns, or if the burns were more extensive, would be due to surgical intervention or to the formation of scar tissue.

It is important to stress that, because of the curvature of the body, third degree burns would in turn be surrounded by areas of second and first degree burning. Since there would be an additional area of flaring, judgment of the extent of flashburning would be complicated. It is also expected that the appearance of flash burns when first seen would be masked by other effects arising from the attack. The blast wave would reach flash burned casualties some time after they were burned. Their burns would almost certainly be soiled by the dust thrown up by the blast wave. Lacerations, contusions, and abrasions might be superimposed. To facilitate the recognition and diagnosis of the flash burns, it would be desirable to cleanse them whenever necessary. In the event of mass casualties, provisions for so doing should hasten the sorting and disposal of such cases.

SUMMARY

Laboratory studies of flash burns in man were undertaken to provide a basis for assessing the range of such injuries from atomic explosions and to study their clinical course and healing time.

Preliminary trials revealed a need to test the influence of the area of skin exposed upon the thresholds for pain, erythema, and blister burning. This test was made by use of a gas fired radiant panel as source. The effects of high intensities of infrared radiation

falling on the skin of the forearm in 1 second were studied in 8 male volunteers. It was found that the threshold intensity for pain and for erythema (first degree burns) was greatly influenced by the size of the aperture used for exposures, but this wide variation did not obtain for the shallow blister burns. The median effective dose for shallow blister burns was found to be 2.0 calories per square centimeter. The clinical course and healing time of these burns are reported.

Further studies of small burns were then undertaken by using a stable carbon arc source of more realistic spectral qualities than the radiant panel. It was found that 2.0, 3.5, 4.8, and 5.25 calories of predominantly white light radiation falling on the skin in less than 0.5 second produced erythema, shallow blister, deep blister, and whole skin loss flash burns, respectively. The clinical courses of these burns are described. The healing times to be expected for uninfected flash burns from 3.0, 4.0, and 5.0 calories of predominantly white light would be 8, 15.5, and 25 days respectively.

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NUTRITIONAL MANAGEMENT IN DUODENAL FISTULA

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THE FREQUENT OCCURRENCE of duodenal fistulas and the high mortality continue in spite of the great advances in surgery. This complication follows approximately 2 per cent of all gastrectomies, and results in 16.5 to 85 per cent mortality, varying with the promptness of diagnosis. Bartlett and Lowell report an over-all mortality of 37 per cent, but only 14 per cent in those cases diagnosed "early." Larsen and Foreman report 11 deaths in 13 cases treated at Western Reserve University, or 85 per cent mortality, and state that only 2 were seen sufficiently early for adequate treatment. Craighead and St. Raymond reported 12 deaths in 22 cases at Louisiana State University School of Medicine, a 66 per cent mortality. Avola and Ellis encountered 13 cases of "duodenal stump leakage" among 621 gastric resections at Boston City Hospital, or an incidence of 2.1 per cent. Ten of these patients, or 77 per cent, died.

Utilization of all precautions and safeguards and maintenance of a high index of suspicion for early recognition are extremely important. The application of rational physiologic treatment with particular attention to nutrition is absolutely essential.

Knowledge of the principal and contributing causes of duodenal fistulas is important in its prevention. Some of the principal causes (technical—usually preventable) are as follows: (1) trauma to the duodenum during upper abdominal surgery causing lateral type duodenal fistula; (This may be an unrecognized injury or perforation caused by retractors or hemostats during surgery.) (2) faulty suture technique following gastrectomy, such as inadequate inversion of the duodenal stump, strangulation ischemia by sutures, and excessive stripping of blood vessels for duodenal closure; (3) faulty gastroenterostomy anastomosis or torsion resulting in obstruction with increased intraduodenal pressure; (4) failure of duodenal closure proximal to an obstructing ulcer; (5) inadequate hemostasis with resulting blood and serum collections about the duodenum; and (6) irritation with necrosis from rubber drains adjacent to the closed duodenal stump. Contributing causes include: (1) extensive scar tissue at the site of duodenal closure adjacent to common bile and pancreatic ducts; (2) local infection about the ulcer; (3) pancreatic activity on absorbable suture material; and (4) malnutrition—with protein depletion and tissue edema, resulting in impaired wound healing.

Lateral duodenal fistulas may result from trauma of abdominal injuries, but most of them occur following difficult surgical procedures on the external biliary tree, duodenotomies, and operations on the right kidney. Extensive pathologic changes in the right upper quadrant of the abdomen can so distort the normal landmarks that utmost care is needed to avoid injuring the duodenum with retractors, hemostats, and sutures.

The more common end type duodenal fistulas follow gastrectomy. Many technical modifications and safeguards in gastrectomy have been suggested to avoid a complicating duodenal fistula. Mobilization of a scarred duodenum with a posterior penetrating ulcer must be tempered with skill and judgment. Excessive stripping of the blood vessels in the duodenal stump during preparation for closure may cause ischemia and strangulation of tissue by tight sutures and may produce necrosis. Mattress sutures placed for control of bleeding near the suture line can so seriously interrupt the blood supply to the duodenal stump that necrosis with fistula formation may be inevitable. No-

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where in surgery will meticulous care and gentle tissue handling pay greater dividends than in the closure of the duodenum which is badly scarred by repeated episodes of acute ulceration. Inadequate closure of the suture line is extremely hazardous.

Tissue drains adjacent to the duodenal suture line interfere with the deposition of fibrin and delay healing. Rather than acting as a safeguard, they may actually contribute to the development of a duodenal fistula. Increased intraduodenal pressure due to obstruction at the gastrojejunal anastomosis from torsion and edema may alone produce disruption of the duodenal stump. This risk may be minimized by passing a previously inserted Levin tube downward through the proximal limb of the gastroenterostomy into the duodenum for constant decompression during the early postoperative period.

Extensive scar tissue, edema, or infection about the ulcer may contribute to the failure of the duodenal closure. Both local infection and pancreatic activity may cause early loss of catgut suture. Leakage and duodenal fistula may result.

When one proceeds unwisely in the duodenal dissection hoping to free a penetrating ulcer from the pancreas and the scarred duodenum from the common bile duct, in order to resect rather than possibly exclude the ulcer area, one may be committed to an unsatisfactory duodenal closure. When such technical difficulties are experienced, a complicating duodenal fistula should be anticipated. It is difficult then to understand why, under such circumstances, an early diagnosis is obtained so infrequently. When a satisfactory closure is not obtained, the insertion of a small catheter through the suture line into the duodenum with its distal end brought out through a stab wound for dependent or suction drainage may be lifesaving. On the other hand, when this procedure is carried out a duodenal fistula is created. The duodenum may leak around the tube or the tube may slip out of the duodenum. Because of this additional hazard we believe that a feeding jejunostomy should be added whenever this procedure is employed. During the operation a previously inserted Levin tube may be passed into the distal limb of the anastomosis for postoperative jejunal feeding. If inadvertently withdrawn postoperatively, its replacement into the jejunum is difficult. Gastric feeding by tube or otherwise is inadequate in the presence of a fistula and may be harmful as it spills through the fistula contaminating the tract and perhaps also the peritoneal cavity.

Malnutrition is the greatest pre-existing cause of postoperative duodenal fistulas. Most patients who require gastric resection for either ulcer or carcinoma also suffer from chronic malnutrition. Many have lost considerable weight and their serum protein level is usually low. Inadequate attention is usually given preoperatively to protein repletion, and gastrectomy is undertaken frequently in the presence of this complication. Postoperatively, the increased urinary nitrogen excretion, due to stress of trauma and the absence of an adequate dietary intake, results in progressive protein depletion. The low tissue protein and the associated tissue edema result in impaired or delayed wound healing. The sutured duodenal stump in such cases may fail in the early postoperative period and result in a duodenal fistula.

It is evident, therefore, that the first effort in the prevention of duodenal fistulas should be the preoperative correction of nutritional deficiences. It is not enough merely to transfuse a protein depleted patient preoperatively and restore the blood volume to normal. It must be stabilized against subsequent contraction as plasma protein may be utilized for other body protein requirements. This restoration of body protein will contribute to the expansion and stabilization of blood volume. The general body protein should be restored as completely as possible before surgery, by forced feeding if necessary. A period of positive nitrogen balance should be established. In the absence of urgent surgery this can be done effectively by continuous 24 hour drip tube feeding. Even in the presence of x-ray

evidence of pyloric or duodenal obstruction we have been able to feed these patients, restore their serum protein level to normal, and establish significant weight gain. In duodenal obstruction a thorough gastric lavage should eliminate all residual food, barium, and viscous material. Antibiotics may be administered to decrease inflammatory edema. The high protein tube feeding solution should then be administered by slow, constant, and continuous drip. Occasional test aspirations should be made until it is determined that the feeding solution is passing through the duodenum. The rate of administration is then gradually increased from 1 to 1½ or 2 liters or more in 24 hours. Ulcer pain is promptly eliminated by the buffer action of the amino acid formula used. Clinical improvement and weight gain are usually very rapid. One to 3 weeks of this regimen of feeding will greatly reduce the risk of postoperative duodenal fistula.

RECOGNITION AND TREATMENT OF DUODENAL FISTULAS

The first prerequisite for adequate treatment of a duodenal fistula is its prompt recognition. The first evidence may be upper abdominal pain or distress following gastrectomy, or systemic evidence of postoperative infection. A sudden rise in temperature and abdominal tenderness with some rigidity are the rule. Adequate drainage for evacuation of spilled duodenal contents from the peritoneal cavity is an absolute necessity, and this complication requires early operative intervention.

If any doubt remains as to the source of the drainage from the wound, one should observe the following characteristics: (1) marked alkalinity of the material; (2) high amylase content; (3) early autodigestion of the surrounding skin and subcutaneous tissue; (4) the appearance of methylene blue, carmine, or charcoal in the fistula following its oral administration.

Once the diagnosis has been made and drainage established, the patient should be placed on a regimen with a basic concept of correction of the pathologic physiology which gives this complication a high mortality.

The continuous loss of duodenal contents, consisting of biliary and pancreatic secretions and a large part of the patient's food intake, is responsible for the high death rate in these patients. The fluid and electrolyte losses can be temporarily corrected by careful intravenous fluid therapy. The cumulative nitrogen losses cannot be corrected in this manner, and the result is starvation malnutrition. This condition develops rapidly since most of these patients are already in a state of protein deficit preoperatively. With progressive protein depletion the body's synthesizing mechanism becomes markedly depressed limiting all physiologic functions, particularly hemoglobin and plasma protein regeneration, cell maturation, and wound healing.

With adequate nutritional management and proper local care very few duodenal fistulas will require surgical closure. Almost all will close spontaneously.

CONTINUOUS DRIP NASOJEJUNAL FEEDING

Intravenous fluid and electrolyte therapy may be effectively continued for only short periods of time. Adequate calories and protein intake are important to correct deficits and to maintain positive nitrogen balance. These cannot be administered in adequate amounts other than by the gastrointestinal tract. Jejunal feeding is, therefore, essential either through a jejunostomy or by a nasogastrojejunal feeding tube. Any compromise by attempting oral feedings, or merely nasogastric tube feeding in presence of profuse duodenal drainage or by prolonged massive intravenous alimentation, will usually fail.

In spite of the continuing loss of fluids, minerals, and proteins by duodenal leakage, the constant drip jejunal feeding regimen (4, 5) has proved adequate in the correction of severe fluid and electrolyte imbalance and the establishment of positive nitrogen balance (8) so necessary for wound healing. It has resulted in clinical improvement, weight gain, and the closure of duodenal fistulas in our 11 patients treated by this regimen.

Feeding jejunostomies were not prepared. Solutions were administered through a fine plastic catheter passed through the nose and stomach into the jejunum. This feeding was accomplished by having the patient swallow a silk or cotton thread with lead shot attached for x-ray identification (Fig. 1). A 3 foot piece of thread is used and the proximal end securely attached to the face with adhesive tape. If it has passed into the duodenal limb of the anastomosis it is withdrawn and reinserted. When the shot has passed through the distal limb of the anastomosis and has been demonstrated by x-ray examination to be in the jejunum, a fine plastic feeding tube is passed through the nose, brought out through the mouth, and attached by its end to the thread with a short piece of heavy chromic catgut. The catgut link permits separation of the thread from the feeding tube after it has been drawn by the thread through the stomach and into the jejunum. Within 12 to 24 hours its position may be verified by x-ray or fluoroscopic examination. If a nonradiopaque feeding catheter is used, lipiodol or a thin barium mixture may be injected for visualization.

The tube feeding solution which we have used is sufficiently thin to pass through a fine feeding catheter by gravity. It is crystal clear, nonviscous, sterile, and bacteria-resistant. It contains 65 grams of protein, consisting of partially hydrolyzed lactalbumin, and 160 grams of dextrose per liter, with all necessary electrolytes and trace minerals. The formula provides 900 calories per liter of solution. Alcohol may be added for sedation or for additional calories, providing approximately 350 calories per 50 cubic centimeters. Vitamins are supplemented by addition to the feeding solution or by injection. During the first 24 hours of tube feeding only 1 liter is administered by carefully controlled constant drip of about 10 to 15 drops per minute. This amount is gradually increased, by not more than 500 cubic centimeters daily, to 1½ or 2 liters or more daily to provide the water, electrolyte, calorie, and protein requirements.

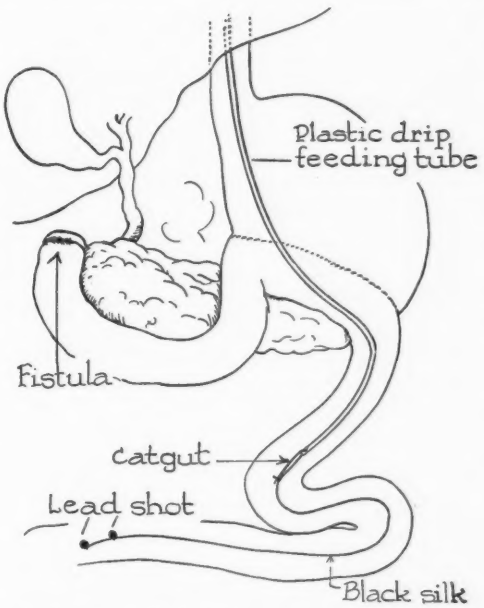

FIG. 1. Method of intubation for continuous nasojejunal tube feeding. Note that the previously swallowed shot-weighted string, which was demonstrated by x-ray examination to be in the distal jejunal loop, has been attached by chromic catgut to the fine plastic feeding tube. The weighted string has drawn the tube from the stomach into the jejunum where it later becomes detached as the catgut separates.

Local treatment of the fistula tract by continuous suction sump drainage through the wound will prevent its enlargement by autodigestion. Skin care with Ladd and Gross paste or other suitable amphoteric or inert paste, such as boiled amphojel, kaolin, or aluminum paste, is important. Banthine in adequate amounts, approximately 100 milligrams every 6 hours, has been credited with decreasing the amount of pancreatic secretion. It has been used in 3 of our cases.

Eleven cases of duodenal fistulas have been successfully treated by this regimen. Positive nitrogen balance was promptly attained, weight gain was rapid, and the fistulas closed in all cases in from 7 to 28 days. Following are 5 cases of the series.

CASE 1 (Fig. 2). J. H., a 46 year old male with chronic alcoholism and a known duodenal ulcer with a previous perforation, was admitted to the hospital

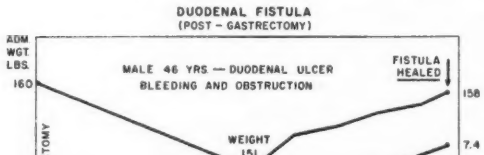

FIG. 2. Continuous nasojejunal tube feeding was begun 3 weeks after development of a duodenal fistula. Graph demonstrates protein restoration, weight gain, and closure of the fistula.

on November 26, 1950, in shock from massive hemorrhage. He was transfused with 2,000 cubic centimeters of whole blood and improved but he soon vomited a large amount of blood and relapsed into shock. He was then transfused almost continuously during the night and was operated upon the following morning. A bleeding penetrating posterior duodenal ulcer was found and a subtotal Billroth II gastric resection was carried out. At operation difficulty was encountered in the duodenal closure so a tissue drain was inserted. The following day an obvious duodenal fistula was recognized. Methylene blue administered orally appeared in the drainage.

Intravenous dextrose and electrolyte solutions were administered and sump drainage was instituted. Liquid diet was begun on the third day and was given in frequent feedings supplemented with amino acids. After 3 weeks on this routine the total serum protein fell from 6.5 to 5.8 grams per cent, and he had lost 9 pounds. Duodenal drainage continued to be profuse.

Continuous nasojejunal feeding was then started through a plastic feeding tube attached to a previously swallowed lead-weighted string passed into the jejunum. Beginning with 1 liter of formula in 24 hours, the volume was gradually increased to 2 and finally to 3 liters, providing 2,700 calories and approximately 200 grams of protein daily. In 26 days of this regimen the patient gained 7 pounds in weight; the serum protein rose steadily to 7.4 grams per cent; the fistula closed and the wound healed.

The intravenous fluids and diet supplemented with amino acid mixtures failed to correct the negative nitrogen balance in this protein-depleted patient with duodenal fistula. Continuous drip feeding, day and night, into the jejunum, of a high calorie, high protein solution was effective in establishing a positive nitrogen balance, restoring the depleted tissue protein, and aiding in the closure of the fistula. The nasojejunal feeding tube was passed as previously described.

CASE 2. L. D., a white male, aged 54 years, was admitted to the hospital June 6, 1951, for gastric resection. He had had 2 perforations 2 years previously and several recent hemorrhages. X-ray examinations revealed a duodenal ulcer.

On the third day after a subtotal Billroth II gastric resection, he suffered severe epigastric pain, abdominal rigidity, and profound shock. He was again operated upon and a disrupted duodenal stump was revealed. The abdomen was closed about a sump drain placed near the duodenal opening for continuous suction. A protective ointment was later applied to the skin about the fistula. Continuous gastric suction and intravenous fluid therapy were begun. His weight fell from 170 to 160 pounds and the serum proteins to 6.0 grams per cent by the seventh day of the fistula.

Continuous drip feeding was started on the eleventh postoperative day. Two liters daily were administered by the nasojejunal route through a fine plastic catheter led into the jejunum by a weighted string. On the fifteenth day of feeding the fistula closed, the serum protein was 6.5 grams per cent, and his weight was 164 pounds.

This patient appeared to be in fairly good nutritional state with no recent weight loss at the time of operation. Loss through the fistula of bile and pancreatic secretions and of orally ingested foods and the increased postoperative urinary nitrogen excretion created a serious negative nitrogen balance. A positive balance was restored and maintained by constant drip feeding of the high protein formula into the jejunum. Healing of the fistula was rapid after a period of restoration of tissue protein.

CASE 3. F. M., a white male, aged 61 years, was admitted to the hospital on June 14, 1952, with a duodenal ulcer of 26 years' duration. He had had a massive hemorrhage in 1934 and frequent attacks of severe epigastric pain. One week prior to admission he had developed duodenal obstruction and vomited all food and liquids.

A subtotal gastric resection was performed on July 2, and difficulty was met closing the duodenum because of extensive scarring around the ulcer. The duodenal stump was closed about an indwelling catheter.

On the seventh postoperative day he suddenly went into shock. There was increased drainage from and about the duodenal catheter. Fluids and electrolytes

were supplied by intravenous therapy which included 50 grams of amino acids twice daily. High calorie liquid diet was given and the duodenal drainage became more profuse.

He became progressively weaker and more emaciated, with pitting edema of the legs and buttocks. The serum proteins fell from 8.25 immediately postoperatively to 5.4 grams per cent with 2 grams per cent albumin on the twentieth day of his fistula. He then developed a complete wound dehiscence which was repaired. Fecal drainage appeared from the duodenal fistula tract, and diodrast injected into the opening revealed a communication with the transverse colon. A right subphrenic abscess was localized and drained on the thirtieth postoperative day. The serum protein was then 4.95 grams per cent and serum albumin 1.8 grams per cent.

Continuous drip nasojejunal feeding was started August 8, the thirty-sixth postoperative day or twenty-ninth day of duodenal fistula and was continued at 2½ liters by constant drip in 24 hours. On the twenty-eighth day of this regimen the fistula was closed and the wound was healed. The total serum protein was 7.30 grams per cent. His nutritional state appeared excellent.

Apparently the protective catheter inserted into the duodenal stump slipped out. Almost unsurmountable complications followed. These consisted of a postgastrectomy duodenal fistula, subdiaphragmatic abscess, communicating colonic fistula, and wound dehiscence with serious protein depletion. Restoration of the body tissue proteins by establishing a strong positive nitrogen balance with continuous 24 hour constant drip enteral alimentation resulted in the restoration of serum and tissue proteins and closure of the duodenal and colic fistulas.

CASE 4. W. O., a 40 year old male, was admitted to the hospital on April 6, 1951, with a recent infection in a laparotomy wound, 2½ years following a gastrectomy for carcinoma. Drainage from the wound had become profuse 1 week prior to admission. The hydrogen ion concentration of the drainage was 8, and methylene blue taken by mouth rapidly appeared in the drainage. The skin became digested, and a diagnosis of duodenal fistula was confirmed by x-ray examination.

He was given banthine and a high protein liquid diet supplemented by amino acids, but he continued to lose weight and become weaker. The serum proteins fell from 7.1 on admission to 5.45, and the drainage remained profuse.

On the fourteenth day after admission constant nasojejunal drip feeding was started and continued for 3 weeks. Drainage ceased and the fistula healed on the twentieth day of the feeding regimen.

A perforated duodenal diverticulum with spontaneous healing was suspected. There was no evidence of recurrent carcinoma clinically or by subsequent x-ray studies. The 24 hour constant drip high protein feeding seemed responsible for the rapid clinical improvement and the closure of the fistula.

CASE 5. M. C., a 68 year old white woman with chronic cholecystitis and recurrent attacks of gallstone colic for 1 year, had lost 25 pounds in weight because of the inability to tolerate an adequate diet. She was given the usual preoperative fluid and blood replacement and was operated upon. A cholecystectomy with exploration of the common bile duct was carried out. The duct was also explored transduodenally, and the ampulla of vater was dilated.

On the tenth postoperative day she developed a duodenal fistula. Drainage was profuse. The serum protein level was 5.75 grams per cent. Parenteral fluids alone were used for 1 week. The drainage remained profuse, and the serum protein fell to 5.2 grams per cent.

Two days later continuous drip nasojejunal feeding was started through a fine plastic catheter which was passed by attaching to a previously swallowed lead-weighted string. The feeding was started with 1 liter the first 24 hours at a constant rate of about 10 to 15 drops per minute and was gradually increased to 2½ liters daily by constant drip. The fistula closed on the eighth day of the feeding, and on the tenth day the serum protein level was 7.86 grams per cent. Albumin and globulin levels were not determined.

This lateral type duodenal fistula has a high mortality. Some method of high protein, high calorie feeding is essential. A surgical jejunostomy for continuous drip feeding is frequently necessary. However, following passage of a shot-weighted string through the stomach and duodenum, past the lateral duodenal fistula, and into the jejunum, a fine plastic catheter, such as we have used, can be readily passed into the jejunum for nasojejunal feeding.

DISCUSSION

Occasionally duodenal fistulas close spontaneously. These are usually small leaks with abscess formation and not associated with previous malnutrition, severe negative balance, and progressive tissue protein deple-

tion. Local treatment alone, such as drainage and the use of antibiotics, is usually credited with these recoveries. The patients with profuse drainage of duodenal contents and loss of much of their oral intake have a severe negative nitrogen balance and develop a rapid loss of body proteins, which is the major factor in the extremely high mortality associated with duodenal fistula. Adequate fluids, electrolytes, and nutrition must be provided and utilized. In these patients we have found the continuous nasojejunal or jejunostomy tube administration of high calorie, high protein feeding solution to be the most logical and efficient method of treatment. We believe that the protein requirements are best met in this emergency by its continual administration throughout the night as well as during the day. The osmotic effect of hypertonic feeding solutions on the jejunal mucosa is minimized by the slow continuous drip method of administration. Nausea and diarrhea commonly associated with protein depletion and forced feeding are thus reduced to a minimum. Institution of this regimen was followed in our patients with duodenal fistulas by a prompt increase in their serum protein level, restoration of normal albumin-globulin ratio, and rapid weight gain.

We have routinely administered 1,000 cubic centimeters during the first 24 hours, adjusting the drip rate accurately by frequent early observations in order to administer slowly and constantly one-third of the total amount during each 8 hours of nursing care. Although varying slightly with the administration drip set utilized, it averages about 10 to 15 drops per minute per liter during 24 hours. An excessive rate of drip is minimized by a special valve insert consisting essentially of a 25 gauge needle hub tied within the tubing. The amount administered is increased 500 cubic centimeters or less daily to 2,500 cubic centimeters. The problems of formula preparation are eliminated by use of the stock feeding solution, and nursing requirement is lessened by continuous rather than fractional feeding. Continuous rather than fractional feeding appears to provide more complete nitrogen retention for maximal tissue protein synthesis.

SUMMARY AND CONCLUSIONS

1. The present status of duodenal fistulas is presented. The immediate and contributing causes are discussed.

2. Protein depletion and fluid and electrolyte losses are emphasized as the most important factors in the pathologic physiology of the patient with a duodenal fistula.

3. A treatment regimen is outlined. This consists, principally, of continuous nasojejunal drip feeding of high protein, high calorie solutions through a fine plastic feeding catheter 24 hours each day and continuing until the fistula closes. Vitamins, antibiotics, sump drainage, and skin care about the fistula opening are discussed.

4. The method of nasojejunal intubation in gastrectomized patients is described.

5. Eleven patients with duodenal fistulas were treated by this method. All survived, their fistulas closing in 7 to 28 days. Five cases are presented.

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THE REDUCTION OF POSTNEPHRECTOMY HYPERTENSION BY RENAL HOMOTRANSPLANT

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THE DEVELOPMENT of the hypertensive state in the nephrectomized dog sustained by dialysis (5) led to attempts to evaluate the influence on the hypertension by renal homotransplants (12). Observations in our laboratory during the past 5½ years have indicated a reduction of the hypertension by renal homotransplants through mechanisms other than those associated with the removal of water and salt by diuresis. Various data supporting this interpretation are presented.

METHODS

Adult mongrel dogs were used (Table I). Purina dog food was fed before the second nephrectomy. The kidneys were removed posteriorly, the first under sodium pentobarbital and the second under ether anesthesia 5 to 7 days later.

The renal transplantation, under ether anesthesia, was made by anastomosing the renal artery and vein and the proximal segments of the severed carotid artery and jugular vein respectively. Continuous everted mattress sutures or over-and-over sutures with No. 5-0 braided silk on an atraumatic needle were used. The ureter was brought to the surface separately.

The time of total renal ischemia varied between 20 and 40 minutes. The donor kidney was made ready under sodium pentobarbital anesthesia; upon separation its vasculature was flushed out with saline containing heparin. The tips of the renal artery and vein of the donor kidney were dipped in 40 per cent formaldehyde for 1 minute before suturing, as suggested by Gross, Bill, and Peirce. No compatibility tests between donor and recipient were conducted.

After the arterial anastomosis, periodic spurts of the recipient's blood were allowed to traverse the donor's kidney. Within 5 to 20 minutes following completion of the anastomosis, urine flowed from the ureteral catheter. The over-all operative time varied between 1.5 and 2.0 hours.

Following the procedure aqueous penicillin (10,000 to 15,000 units per day) was injected parenterally. Terramycin (100 mgm. daily) was given orally or parenterally. At the termination of the operation, 9 of the 16 animals were given a blood transfusion, the volume varied between 7 and 33 cubic centimeters per kilogram (average, 18 c.c./kgm.). The blood was usually cross matched by means of the indirect Coombs test, using canine antiglobulin serum prepared in this laboratory (17). The transfusion was given to replace erythrocytic deficiency due to uremia (21) as well as operative blood loss. Seven dogs did not receive an infusion of blood.

The dietary formulas used consisted of a mixture of dialyzed peanut oil, pure dextrose, electrolyte-free casein, and a vitamin supplement previously described (23). The diets are listed as follows:

Content	*Diet 1*	*Diet 2*	*Diet 3*
Calories per 100 cubic centimeters	530	620	430
Fat, per cent	67	62	41
Carbohydrate, per cent	22	33	37
Protein, per cent	11	5	22

The first 7 dogs received diet 1, the next 2 diet 2, and the last 7 dogs received diet 3. Between 150 and 200 cubic centimeters of

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TABLE I.—DATA OBTAINED FROM DOGS RECEIVING RENAL HOMOTRANSPLANT WHILE HYPERTENSIVE FOLLOWING BILATERAL NEPHRECTOMY

Dog No.	Wt., kgm.	Diet No.	Irrigation, L./24 hrs.	Blood transfusion c.c./kgm.	Control BP, mm. Hg	Change BP, mm. Hg Before	Change BP, mm. Hg After	Duration change BP, days	Estimated urine flow, L./24 hrs.	Wt. change, kgm. Before	Wt. change, kgm. After	Day of transplant	Survival, days
1	13.2	1	6	16	115	+45	+20	5–7	2.4	+1.4	+1.2	11	21
2	14.2	1	6	30	115	+55	+15	7	1.5	+0.8	+0.2	10	32
3	18.4	1	6	10	125	+30	+5	7–10	0.7	−0.7	−2.8	11	37
4	15.2	1	6	10	105	+70	+10	7		+0.1	−0.3	12	22
5	7.0	1	3	7	105	+40	0	7–9	1.2	+0.8	+0.6	11	24
6	26.8	1	6	14	125	+25	0	5	1.5	−1.4	−1.4	15	23
7	8.6	1	3	20	115	+50	+20	3	2.1	−0.2	−0.4	8	14
8	14.0	2	3		120	+40	+20	2–3	1.2	+0.3	−0.8	7	13
9	10.8	2	2		115	+45	+20	1–2	1.2	−0.8	−0.6	9	23
10	12.5	3	3		120	+60	+15	2–5	0.9	+1.1	+0.7	7	20
11	8.4	3	2		115	+55	+10	4	1.0	−0.2	+0.7	9	16
12	9.9	3	2		115	+45	+20	3	1.4	−0.3	−0.3	8	22
13	13.0	3	3		112	+28	+8	5	1.5	−0.3		4	11
14	14.5	3	2		117	+38	+3	2	1.4	+0.5	0	7	10
15	12.7	3	2	23	125	+50	0	3	1.9	+0.6	+0.6	7	17
16	13.4	3	2	30	120	+50	0	3–4	0.7	0	−0.6	5	12
Av.	13.5		3.5	18	117	+45	+11	4–5	1.3			8.8	20

Diets numbers 1, 2, and 3 are described in the text under "methods."
By "irrigation" is meant the volume of fluid placed in and removed from the peritoneal cavity.
The blood transfusion was given shortly after the renal transplantation.
Columns 6, 7, 8, and 9 contain the control mean arterial pressure before the second nephrectomy, the elevation of the pressure before the transplant, the maximal drop of the arterial pressure after the transplant, and duration of the receded BP.
By "wt. change" is meant the change in body weight from the prenephrectomy control before the transplantation when the arterial pressure was elevated and after the transplantation when the pressure had receded maximally.
The "day of transplant" and the "survival in days" are dated from the day of the second nephrectomy.

the formula were given orally per day. This regimen was well tolerated until near termination.

The rate of urine flow per day was estimated from rates observed during several 30 minute intervals of urine collection taken while the dog lay quietly.

The mean arterial pressure was determined by direct femoral artery puncture using an 18 or 19 gauge needle and a mercury manometer. The blood and urine urea concentrations were determined by the method of Taylor and Blair. The urine specific gravity was estimated with a standardized clinical urinometer. The chloride concentration was determined by the method of Van Slyke and Hiller. The serum sodium and potassium concentrations were determined by two approaches, the method of Butler and Tuthill for sodium, the method of Jacobs and Hoffman for potassium, and later the Baird and associates flame photometer for both ions. The body weight was determined each morning prior to feeding and after the peritoneal fluid used in the irrigation had been removed. The scale used reproduced control weights of ±0.15 kilogram.

In the determination of the distribution of radiosulfate 4 to 5 cubic centimeters of the sodium sulfate solution were injected intravenously under vision. The radioactive sodium sulfate as obtained from Oak Ridge was diluted in buffered physiologic saline (*p*H 7.4) to yield 50 to 100 millicuries in the 4 to 5 cubic centimeters. Serum samples were obtained at 30 minutes, and 1, 2, 3, and 4 hours after the injection. The radioactivity in the serum, determined by 2 methods—our own (18, 19) and that developed by Swan and associates—plotted on semilogarithm paper resulted in a slight rectilinear slope. During the distribution of the radiosulfate the ureter was clamped, the activity of the urine in the renal pelvis was subtracted from the injected dose (a minor correction of less than 1 per cent).

The plasma volume was determined in certain experiments by the T-1824 method as described by Mayerson, Lyons, Parsons, Nieset, and Trautman while in other experiments the blood volume was determined with radiochromium according to Sterling and Gray.

Peritoneal irrigation was conducted as previously described (23). Exchanges of 3 to

6 liters per day were obtained. The irrigation fluid had the following ionic concentrations in milliequivalents per liter: Na 141, K 2.7, Ca 3.6, Mg 1.5, Cl 108, HCO_3 41. A 10 to 20 per cent positive fluid balance accrued in most experiments prior to the homotransplantation.

The tissues obtained at postmortem examination were fixed in 10 per cent formalin; paraffin blocks were cut at 5 microns and stained with hematoxylin and eosin. The wall thickness to lumen ratio (W/L ratio) of small arteries and arterioles of the viscera was measured in a manner similar to that described by Kernohan, Anderson, and Keith. Vessels cut squarely, either round or oval, were measured. Two perpendicular outside and inside diameters were measured and each averaged. A microscale in the eyepiece standardized by a standard scale on a cover slip was used. The difference between the averaged outside and inside diameter divided by 2 gave the wall thickness $\left(\frac{OD-ID}{2}=W\right)$, and W/ID = wall thickness to lumen ratio (W/L).

Fifty small arteries and arterioles from each dog with a homotransplant were measured, making 800 vessels available for analysis. These measurements were compared with those of 440 small arteries and arterioles from 21 normal dogs. Vessels from the gastrointestinal tract, heart, periadrenal area, urinary bladder, brain, liver, omentum, and skeletal muscle were measured.

Plan of experiment. One kidney was removed and the mean arterial pressure was determined daily for 5 to 7 days. The average of these pressure readings, which varied between 110 and 125 millimeters of mercury, was taken as the control pressure. All subsequent blood pressure readings were related to this average figure.

Peritoneal irrigation was begun after the removal of the second kidney; it was continued throughout the remainder of the experiment. A significant hypertension developed in all 16 animals (BP +25 to +70 mm. Hg, average +45 mm. Hg above the control). The homotransplantation occurred 4 to 15 days after the second nephrectomy (average 8.8 days). After the renal transplantation 3 procedures assured a continuation of a positive salt and water balance: (1) The peritoneal irrigation assured an excessive quantity of water and electrolytes by this route at all times. (2) The estimated daily urinary volume was replaced parenterally as isotonic sodium chloride. (3) The dietary formula was continued, and water ad libitum was presented. The amount of potassium in the irrigating fluid and diet was increased since a source of potassium loss existed by the transplant.

Control autogenous renal transplantations. Renal autotransplantation afforded a means of comparing the results of the technique of transplantation as conducted in our laboratory with the information on renal transplants available in the literature. By this means the influence of the transplantation per se on the animal's arterial pressure was evaluated.

Two renal autotransplantation procedures were conducted. In one procedure a kidney was transplanted to the neck of the same animal while the other kidney was left intact for 10 to 21 days, at which time the normal kidney was removed. In the second procedure one kidney was removed and discarded, and immediately the other kidney was transplanted to the neck of the same animal.

Results from 4 animals subjected to the first procedure are summarized diagrammatically in Figure 1. These animals survived 15 days, 35 days, 4 months, and 12 months beyond the removal of the normal kidney. All kidneys displayed pyelonephritis.

The specific gravity of the urine from the transplant remained below 1.010 until the normal kidney was removed, following which it was elevated to 1.016. A higher value was not observed. The urine urea concentration from the transplant was low (0.08 to 0.6 per cent) until the normal kidney was removed, following which it was elevated to normal values (1 to 2 per cent,

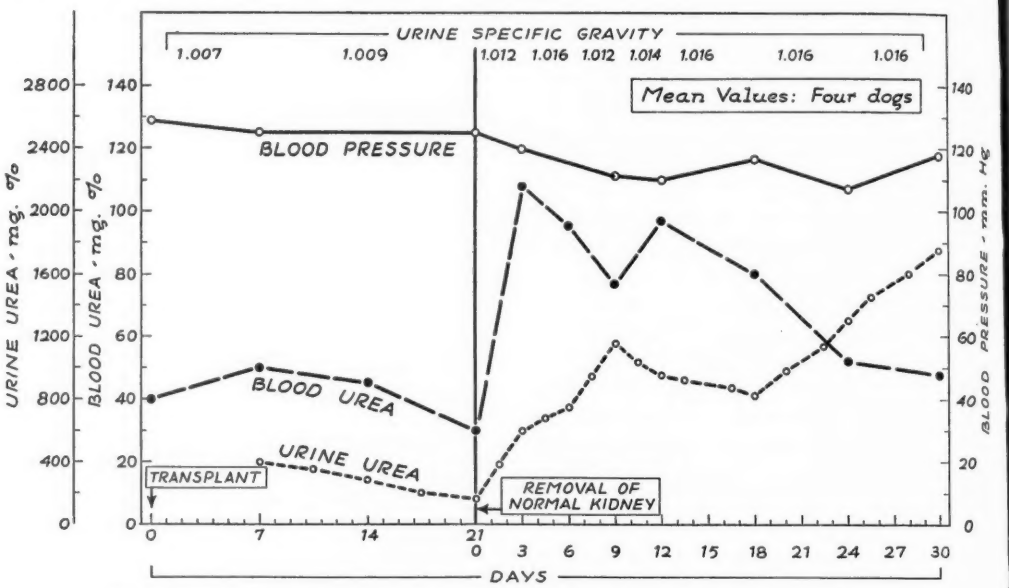

FIG. 1. Various data obtained from dogs subjected to the first type of autogenous renal transplant are depicted graphically. One kidney was transplanted to the neck, the other was left intact for 21 days and then removed. A discussion and the interpretation of these data are given in the text.

average 1.7 per cent), but this ultimate elevation required 4 to 16 days. The chloride concentration of the urine from the transplant remained similar (10 to 96 mEq./L., average 45 mEq./L. before the removal of the normal kidney, and 7 to 94, average 50 mEq./L. after). The estimated urinary flow varied between 1.0 and 1.6 liters per 24 hours.

The blood urea concentration remained at the control level (20 to 70 mgm. per 100 c.c., average 40 mgm. per 100 c.c.) until the removal of the normal kidney when the concentration was transiently elevated (62 to 180 mgm. per 100 c.c., average 105 mgm. per 100 c.c.). The blood urea returned to control levels within 9 to 21 days. The plasma chloride concentration remained normal throughout the entire course (before 98 to 107 mEq./L., after 97 to 109 mEq./L.). Thus, the urine urea to blood urea ratio using the urine from the transplant was depressed (5 to 8:1) before the removal of the normal kidney and remained prominently depressed (5 to 10:1) for 15 to 20 days. Thereafter this ratio was elevated to about 40:1. The elevation of the urea ratio coincided with the return of the blood urea concentration to the control level. The plasma chloride to urine chloride ratio, using the urine from the transplant, remained steady throughout, varying between 2.0:1 and 2.7:1.

The body weight decreased by 0.2 to 0.6 kilogram prior to the removal of the normal kidney. A further steady decrement in body weight of 1 to 2 kilograms for 15 to 20 days occurred after the removal of the normal kidney; thereafter the weight returned to the control level.

Bacteriologic study of the urine, even during prolonged survival, revealed the persistence of Proteus vulgaris. In addition, the dogs succumbing to pyelonephritis earlier had streptococci and staphylococci in the urine.

The mean arterial pressure remained at the control level throughout the procedure.

Five dogs were subjected to the second autotransplantation procedure. Three dogs

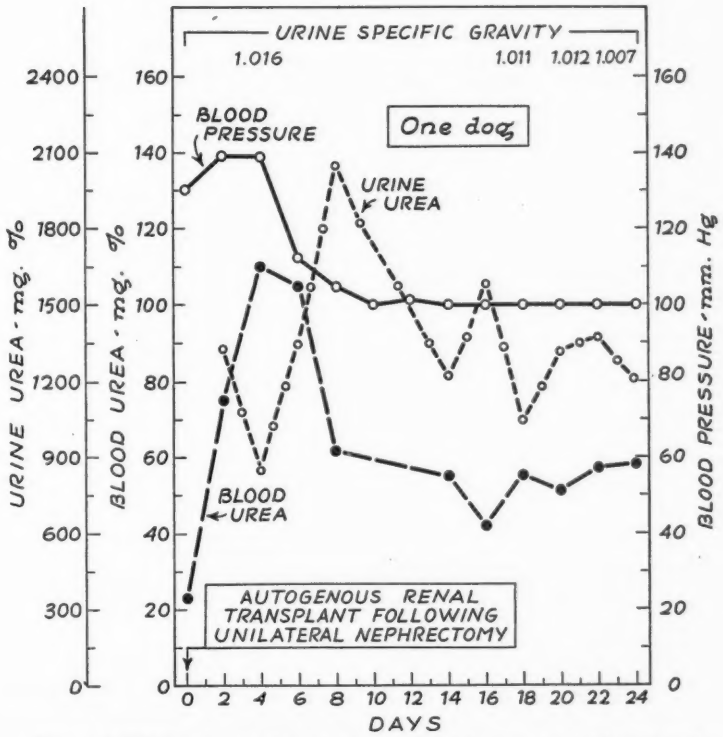

FIG. 2. Graphic representation of data obtained from a dog subjected to the second type of renal autotransplantation. One kidney was removed and discarded and the other kidney was transplanted to the neck. The text contains a discussion of these data.

succumbed after 6 and 7 days. One dog survived 15 days, and 1 dog survived 30 days.

Figure 2 summarizes the results of one of the experiments. The specific gravity of the urine remained depressed in this example although in another experiment it was elevated to 1.022. The urine urea concentration was elevated from 0.9 to 2.0 per cent within 9 days. The chloride concentration of the urine varied between 7 and 50 milliequivalents per liter, average 23 milliequivalents per liter. The estimated urine flow varied between 0.62 and 2.3 liters per 24 hours (average 1.2 liters).

The blood urea concentration was elevated for 8 to 14 days. The plasma chloride concentration remained normal (96 to 106 mEq./L.). The urine urea to blood urea ratio remained depressed (8 to 12:1) for 8 days but thereafter it was elevated to 33 to 38:1. The plasma chloride to urine chloride ratio varied between 2:1 and 4.7:1 for 8 days and thereafter was elevated to 5:1 to 15:1. The body weight steadily decreased to —4.0 kilograms by 24 days.

The mean arterial pressure was transiently elevated. The elevation remained for about 7 days. For all 5 dogs the elevation averaged +25 milligrams of mercury above the control value. After its recession the blood pressure remained normal thereafter.

Summary of results of the renal autotransplantations. These observations with the autotransplantation of kidneys indicated that the transplantation procedure per se, as conducted in this laboratory, was associated with a mild recoverable form of renal insufficiency lasting 1 to 3 weeks. The evidence

TABLE II.—DATA ON NEPHRECTOMIZED DOGS SUBJECTED TO SHAM PROCEDURE

Dog No.	*Wt., kgm.*	*Diet No.*	*Irrigation, L./24 hrs.*	*Blood transfusion, c.c./kgm.*	*Control BP, mm. Hg*	*Change BP, mm. Hg*		*Wt. change, kgm.*		*Day of operation*	*Survival, days*
						Before	*After*	*Before*	*After*		
1	14.0	1	6	18	110	+40	+60 +50 +40 +30	+0.8	+1.2	12	16
2	11.4	1	3	26	105	+45	+20 +20 +45 +65 +25	0	−0.3 −0.1 −0.3 −0.3	8	14
3	11.4	1	3	17	123	+47	+47 +57	0	+0.4 −0.2	9	11
4	14.1	3	2		115	+45	+45 +35 +35	+1.3	+1.6	6	10
5	13.3	3	2		115	+45	+60 +60 +60 +80 +85	+1.8	+1.7 +1.7 +1.2	5	10
Av.	12.8		3	20	114	+44	+46 +44 +45	+0.8	+0.9 +0.5	9	12

The various columns contain the same type of data as in Table I.
The change in the mean arterial pressure after operation is related to the control level and the figures in the column represent the daily values after the sham operation. The arterial pressure was sustained in all but dog No. 2 in which there was a transient lowering.

supporting this conclusion included a transient azotemia, a lowered urine to blood urea ratio, a lowered urine specific gravity, and a transient loss of weight. The changes were similar to those due to an acute tubular injury following renal ischemia in situ. In the absence of normal renal tissue this transient renal insufficiency was associated with a transient mild hypertension.

Control sham operation. Five dogs were subjected to a sham procedure. The procedure consisted of the removal of one kidney, determination of the control blood pressure for 1 week, removal of the second kidney, maintenance for 5 to 10 days on peritoneal dialysis until a fixed hypertension occurred. At this time the animal was maintained under ether anesthesia for the same period as required for the renal homotransplant, namely 1.5 to 2.0 hours. The incision was made in the neck and all manipulations of the transplantation except the attachment of the kidney were performed. Then the wound was closed. The animal was maintained by dialysis and fed the same diet as following the homotransplantation.

Figure 3 depicts diagrammatically the state of the mean arterial pressure and body weight while Table II summarizes the results with these animals. The arterial pressure was elevated within 5 to 12 days to an average of 44 millimeters of mercury above the control value. After the sham procedure the blood pressure remained elevated for 2 to 5 days, then the animals succumbed. The body weight remained the same or was slightly elevated.

At autopsy these animals displayed severe widespread acute cardiovascular necrosis as previously described in certain nephrectomized preparations. The degree and extent of the cardiovascular injury exceeded any previously encountered by us for the same period of time. The impression was gained that factors related to the operative procedure accentuated the cardiovascular injury when the kidneys were absent.

RESULTS

Sixteen dogs were subjected to bilateral nephrectomy, dialysis, and subsequently a homogenous renal transplantation.

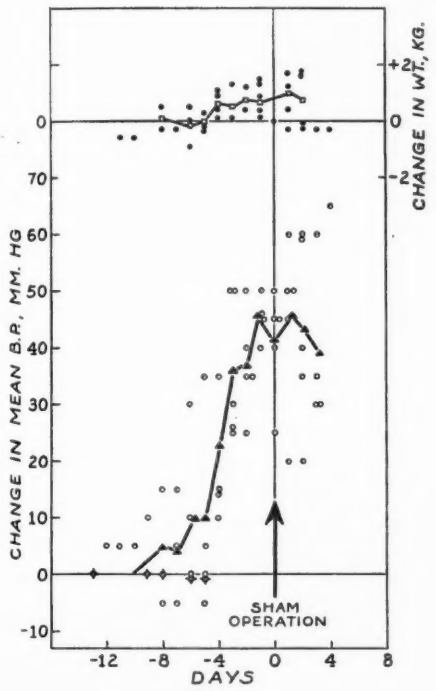

FIG. 3.

FIG. 3. Diagrammatic representation of the changes in mean arterial pressure and body weight of the dogs subjected to a sham operation. The heavy circle with spikes represents the day on which the second nephrectomy was performed.

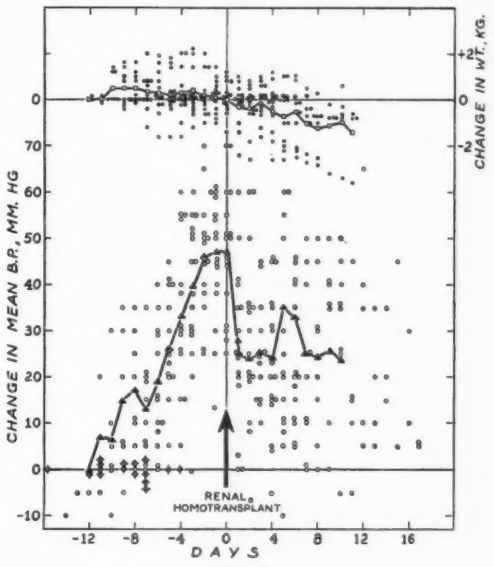

FIG. 4.

FIG. 4. Changes in mean arterial pressure and body weight of dogs subjected to a renal homotransplantation. The heavy circles with spikes represent the day of the second nephrectomy. Beyond the seventh day following the transplant the mean value of the blood pressure became less significant since the pressure was labile, elevated and lowered values were obtained as shown in this graph.

Effect of homotransplant on the hypertension. Figure 4 is a scattergram which relates the state of the mean arterial blood pressure in all 16 experiments. Upon the application of the homogenous renal transplant from a healthy donor the mean arterial pressure in each case receded sharply. The blood pressure recession was usually noted within 4 to 6 hours but in some animals it was not detected for 24 hours. The range of the arterial pressure during the first 24 hours varied between +20 and +50 millimeters of mercury above the control. The average pressure was +11 millimeters of mercury above the control, representing a mean recession of —34 millimeters of mercury in the mean arterial pressure. The mean arterial pressure receded to the control value in 5 instances.

The lowered pressure remained in most instances for 4 to 5 days, after which the pressure became labile, fluctuating between the levels prior to the transplantation and those near the control level. The labile pressure remained for 1 to 2 weeks; thereafter the animals deteriorated. Death supervened 1 to 4 weeks after the transplantation.

During the first week and corresponding to the time that the arterial pressure was lowered, the renal transplant appeared to enlarge and become firm. At about 7 days the transplant began to decrease in size. The urine flow remained prominent (0.7 to 2.4 liters per day) for 1 week, thereafter it decreased and ceased altogether during the third week. Thus the labile pressure and the return of the hypertension corresponded to the time of advanced gross deterioration of the transplanted kidney.

Body weight. Figure 4 also depicts the state of the body weight of these animals. There

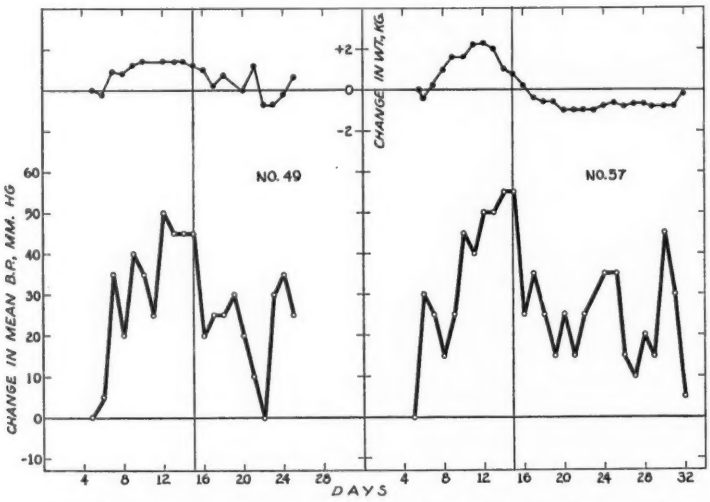

FIG. 5. Changes in mean arterial pressure and body weight of dogs Nos. 49 and 57. These correspond to dogs Nos. 1 and 2 respectively of Table I. The sustained lowering of the hypertensive state without a corresponding sudden change in the body weight is shown. The graph begins with the day of the second nephrectomy. The vertical line represents the time of the renal homotransplantation. The days on the horizontal axis may be considered relative to the transplantation.

was a steady loss of weight of most animals throughout, but a sudden change in weight did not occur when blood pressure receded.

Figure 5 relates results with individual cases. With dog No. 49 the body weight was elevated (+1.5 kgm.) before the homotransplant and remained above the control level while the arterial pressure was lowered. With dog No. 57 the body weight steadily receded before the renal transplantation. There was no sudden change in body weight at the time of the prominent drop in arterial pressure.

TABLE III.—DATA INDICATING A POSITIVE FLUID BALANCE DERIVED FROM THE FLUID USED IN THE PERITONEAL IRRIGATION

	Positive peritoneal fluid load, liters Change B.P., mm. Hg Change wt., kgm.			*Total fluid load, liters*	*BP after homotransplant, mm. Hg*
Dog No.	*Days 1–4*	*Days 5–8*	*Days 9–12*		
1	+3.6 L.	+2.7	+2.5	+8.8	
	+20 mm. Hg	+50	+45		+20
	+0.7 kgm.	+1.4	+1.4		
2	+3.0 L.	+2.1	0	+5.1	
	+25 mm. Hg	+50	+55		+15
	+1.7 kgm.	+2.0	+1.1		
3	+4.0 L.	+4.6	+1.9	+10.5	
	0 mm. Hg	+25	+30		+5
	−0.8 kgm.	−0.2	−0.7		
4	+3.5 L.	+1.8	+0.6	+5.9	
	+30 mm. Hg	+55	+70		+10
	+0.8 kgm.	+0.1	+0.1		
6	+3.7 L.	+2.0	+3.4	+9.1	
	−5 mm. Hg	+5	+25		0
	+0.2 kgm.	+0.9	−1.4		

The gain in weight, when it occurred, was not commensurate with the gain in fluid suggesting a loss of body substance. Despite the positive fluid balance the renal homotransplantation was associated with a lowering of the hypertension without a sudden change in weight. The dogs correspond to those in Table I with the same numbers.

Six dogs were allowed to accrue a positive fluid balance through the peritoneum of 5 to 10 liters prior to the renal homotransplant (Table III). This water and salt load was not associated with a commensurate weight gain apparently due to the concomitant loss of body substance (22). Despite this fluid load and in association with no sudden weight loss the renal homotransplant caused a sustained lowering of the hypertension. These findings lend additional emphasis to the conclusion that the lowering of the blood pressure was not due to the drain of water and salt from the body by the renal transplant.

Function of the renal homotransplant. Figure 6 relates certain studies of the renal function

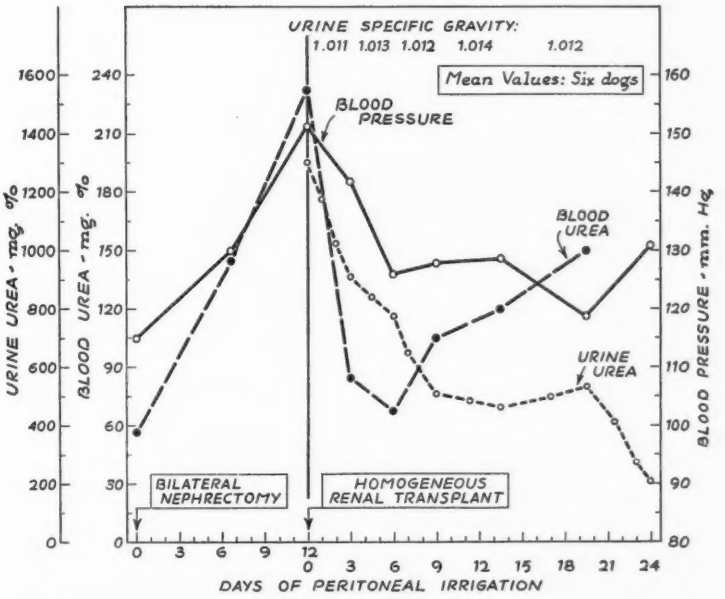

FIG. 6. Various data obtained from dogs Nos. 1 to 6 in Table I dealing mainly with the functional state of the renal homotransplant.

of the first 6 dogs in the present series of 16 dogs subjected to the homotransplantation. The mean values are given.

The specific gravity of the urine from the transplant remained lowered throughout (1.011 to 1.012). The urine urea concentration receded steadily from 1.3 per cent on the first day to 0.5 per cent by 7 days and 0.21 per cent by 21 days. The urine chloride concentration averaged 73 to 99 milliequivalents per liter but varied markedly from dog to dog (17 to 140 mEq./L.).

The blood urea concentration was elevated from 73 milligrams per 100 cubic centimeters before the second nephrectomy to 235 milligrams per 100 cubic centimeters before the homotransplantation. After the transplantation it sharply receded to 65 to 85 milligrams per 100 cubic centimeters and remained lowered for 6 days. Then, during the following 15 days, it gradually returned to 150 milligrams per 100 cubic centimeters. The plasma chloride concentration remained normal throughout the observations (104 to 108 mEq./L.).

The urine urea to blood urea ratio changed from 5.5:1 on the first day to 11.5:1 from the third to the seventh day. Thereafter this ratio gradually dropped to 1.4:1 by 21 days. The plasma chloride to urine chloride ratio was 1.5:1 for 7 days, thereafter it changed to 1:1 by 21 days.

The estimated urine flow varied between 0.7 and 2.4 liters per 24 hours for 7 days. Then it receded to extreme oliguria by 16 days. The estimated 24 hour urine urea output varied between 12 and 23 grams for 7 days when it receded to about 5 grams per day for another 7 days following which the urea output virtually ceased.

These observations indicate a gradual deterioration of excretory renal function from the outset of the homotransplantation. Despite this type of renal deterioration the temporary recession of the hypertensive state occurred.

The influence of electrolyte and water balance before the transplantation. In 2 dogs (Nos. 11 and 12, Table I) the input and output of fluid through the peritoneal cavity were

TABLE IV.—RADIOSULFATE SPACE (S^{35}) AND BLOOD VOLUME (CR^{51}) BEFORE AND AFTER THE RENAL HOMOTRANSPLANT

			Radiosulfate (S^{35}) space				*Blood volume Cr^{51}*			
Dog No.	*Time*	*Wt., kgm.*	*Whole serum method, c.c.*	*Body wt., per cent*	*$BaSO_4$ ppt. method, c.c.*	*Body wt., per cent*	*Volume, c.c.*	*Body wt., per cent*	*Hemat., per cent*	*Mean arterial BP, mm. Hg*
14	Before transp.	14.3	3112	21.7	3002	20.9	1288	8.99	49.0	(117)
	After transp.	14.5	3583	24.6	3619	24.9	1315	9.04	20.6	+38 +3 (−35)
15	Before transp.	12.7	2462	19.4	2341	18.4	1049	8.25	46.0	(125)
	After transp.	13.6	2886	21.2	2851	20.9	1247	9.15	12.5	+50 0 (−50)
16	Before transp.	13.4	2610	19.5	2514	18.7	1302	9.7	43.0	(120)
	After transp.	12.8	2690	21.0	2680	20.9	1431	11.1	17.0	+50 0 (−50)

The corresponding state of the mean arterial pressure is also tabulated. The dogs are the same as those in Table I with the same numbers.

kept equal until the mean arterial pressure was elevated to its utmost. At this time the serum sodium and potassium concentrations were elevated over the values immediately after the second nephrectomy. The blood volume by the dye method was reduced by 6 and 30 per cent. The radiosulfate "space," measured as described earlier (18, 19), was lowered by 6 and 30 per cent respectively. At this time, 4 days after the second nephrectomy, the mean arterial pressure exceeded the control value by 30 and 25 millimeters of mercury. Despite the stringent water and electrolyte balance the arterial pressure continued to rise to +55 and 60 millimeters of mercury above the control. There was only 1 bout of emesis with each dog.

On the eighth and ninth days after the nephrectomies a renal homotransplant caused recession of the mean arterial pressure of 40 and 30 millimeters of mercury. As the arterial pressure receded these animals were allowed to gain weight by the accumulation of water and salt. Thus it was not necessary for the organism to accumulate water and salt from the outside prior to the renal transplantation for the elevation of the arterial pressure to occur, nor was a positive fluid load necessary for the recession of the blood pressure to proceed under the influence of the renal transplant.

The distribution of radiosulfate (*Table IV*). The radiosulfate "space" was measured before the transplant and at the time of the maximal recession of the arterial pressure after the transplantation. The radiosulfate space after the renal homotransplantation, at the time the arterial pressure was lowered, was either equal to or slightly higher than before the transplantation when the pressure was elevated. Thus, by this approach, the lowering of the pressure occurred without concomitant changes in the "extracellular fluid volume" as measured with radiosulfate. These findings correlate with the minimal changes in body weight observed during the same interval.

The values for the radiosulfate "space" obtained by the whole serum method were comparable to those obtained by the precipitation procedure (Fig. 7).

Blood volume (*Table IV*). The blood volume as estimated by the radioactive chromium method was slightly higher at the time the arterial pressure was lowered than before the renal transplantation. Thus the changes in pressure did not appear to be due to changes in circulating blood volume.

A marked lowering of the hematocrit reading after the transplantation indicated a prominent anemia. This occurred whether a blood transfusion was given at the time of the operation or not. The anemia eventually became outstanding and appeared in part to be associated with the absorption of the homotransplant (16).

Vascular lesions. The wall to lumen (W/L) ratio of the small arteries and arterioles

from the viscera of normal dogs varied between 0.1 and 1.6. The small arteries and arterioles included in these measurements had external diameters varying between 50 and 250 microns (80 per cent between 50 and 150 microns).

The frequency distribution of the normal W/L values described a skewed curve on regular co-ordinate scale. Use of the logarithm of the frequency distribution yielded the normal curve. With the latter the logarithm of the mean and standard deviation, and the mean values were obtained (Table V). The mean value was 0.394.

The frequency distribution of the W/L ratio of similar vessels from the series subjected to renal homotransplants yielded a similar skewed curve (Fig. 8). The outside diameters of these vessels varied between 50 and 300 microns (80 per cent between 50 and 150 microns). For all 16 dogs with transplants the W/L ratio varied between 0.1 and over 4.0. Treated in the same manner as the normals the mean value was 0.575. Thus, following the sequence of bilateral nephrectomy, hypertension, and renal homotransplantation, the W/L ratio of small visceral arteries and arterioles was significantly elevated over the normal values.

A difference was observed in the W/L ratio of small arteries and arterioles of the transplanted dogs surviving 11 to 17 days after the bilateral nephrectomy and dogs surviving over 20 days. In the former group the frequency distribution and mean value were not significantly different from the normal, while in the animals surviving over 20 days there was a significant elevation of these values (Fig. 8, Table V).

The elevated W/L ratio resulted from thickening of the arteriolar wall as a result of three major alterations, namely, an apparent hypertrophy of the smooth muscle of the media; hyalinization and thickening of the wall, mainly the media but also the intima; and an increase in cellularity involving all layers but particularly the adventitia and intima apparently due mainly to the deposition of connective tissue. These

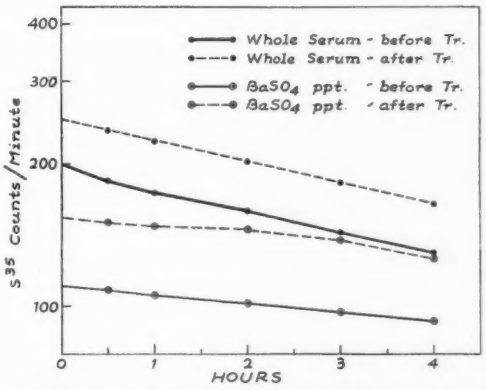

FIG. 7. Dog No. 15, Table IV. Slope of disappearance of radiosulfate during the measurement of the radiosulfate space as obtained by the 2 methods of measurement before and after the renal homotransplantation. The number of counts per minute as extrapolated for equilibrium do not have specific meaning since different volumes of sample of serum were used in the 2 methods. The slopes indicate reproducibility before and after the transplantation and strengthen the position of the measurement of the radiosulfate space as an indication of no excessive loss of water and salt at the time of the reduction of the hypertension.

changes constitute indications of arteriolar disease of the hypertensive cardiovascular type.

These data indicate that advanced arteriolar disease occurred after the interval of maximal destruction and absorption of the renal transplant, and in association with a return of the hypertensive state to its fullest extent. Prior to this time little or no arteriolar disease was observed. Under other circumstances advanced arteriolar disease has been noted 10 to 20 days after bilateral nephrectomy. The data herein presented suggest a protective influence of the renal homotransplant on the arteriolar disease following bilateral nephrectomy. Additional controls, however, are considered necessary before this feature can be considered definite.

COMMENT

A rapid and sustained reduction of the hypertension following nephrectomy of the dog mediated by a homogenous renal transplant has been demonstrated. The lowered blood pressure did not result from the loss

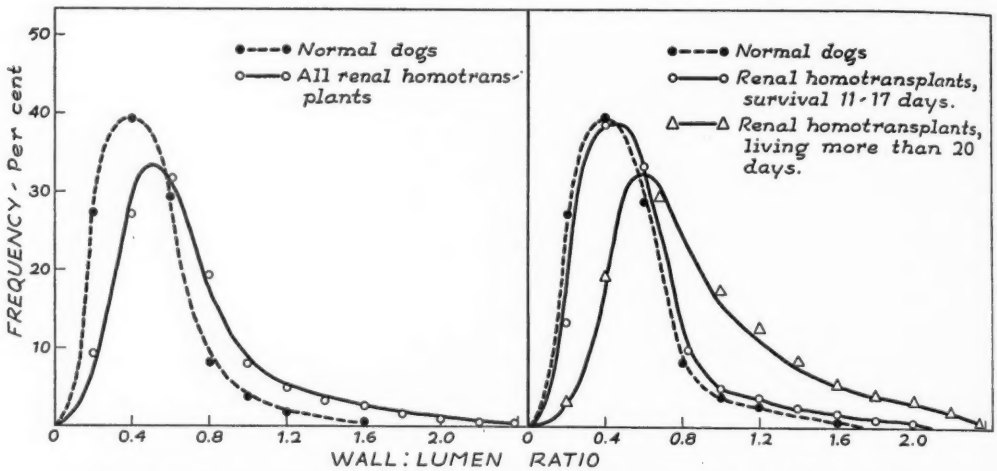

FIG. 8. The frequency distribution of the wall thickness to lumen ratio (W/L) of small arteries and arterioles. The left panel contains data from normal dogs and all 16 nephrectomized dogs which were subjected to a renal homotransplant. The right panel has data from the normal dogs, transplanted dogs living 11 to 17 days, and transplanted dogs living more than 20 days.

of water and salt by diuresis. This conclusion was indicated by the adequate replacement of water and salt by mouth and parenterally, the concomitant lack of a sudden change in body weight, and measurements of the "extracellular fluid volume" and of the blood volume which indicated no major volume changes in these fluid compartments.

The hypertension and cardiovascular lesions of the dog following nephrectomy appear to be aggravated by dietary protein and the excessive intake of sodium salts. Maintenance of sodium balance does not prevent the hypertension (20), particularly when the dietary protein is maintained (14). The renal homotransplant was capable of affecting a reduction of the hypertension either in the presence of rigidly maintained sodium and water balance or in the presence of various loads of water and salt. Moreover, the continuation of dietary protein did not deter the reduction of the hypertension.

The sustained hypertension of the sham operation animals indicated that the operative procedure was not responsible for the reduced hypertension. The earlier demise and the extensive cardiovascular lesions of the sham group suggested protection of the cardiovascular system by the transplant. Measurement of the ratio of the wall to the lumen of small arteries and arterioles strengthened this possibility. An elevation of this ratio is an indication of arteriolar disease. Dogs surviving 11 to 17 days following nephrectomy and 6 to 10 days following the renal transplant revealed minimal or no

TABLE V.—DATA ON THE WALL TO LUMEN RATIO OF SMALL ARTERIES AND ARTERIOLES

Group	*No. of dogs*	*No. of arterioles*	*Range W/L ratio*	*Log. mean*	*Log. S.D. ±*	*Mean*	*p vs. normal*
Normal	21	440	0.1—1.6	0.59584	0.2045	0.394	
BN—homotransplant (all dogs)	16	800	0.1—4.0+	0.75933	0.2699	0.575	<0.001
BN—homotransplant (14–17 days survival)	7	350	0.1—2.0	0.58046	0.3744	0.381	0.5<p<0.4
BN—homotransplant (over 20 days survival)	9	450	0.1—4.0+	0.85221	0.2159	0.711	<0.001

The collective data for all dogs with transplants indicated a significant elevation of the ratio. However, dogs surviving 17 days or less did not reveal a significant change in the ratio while those surviving over 20 days yielded an outstanding elevation. BN indicates bilateral nephrectomy.

arteriolar disease. In the absence of a renal transplant arteriolar disease is usually definite during this interval under the circumstances of these experiments.

The transplantation procedure per se appeared to cause a transient excretory renal insufficiency of autogenous renal transplants. The deterioration of excretory function was continuous with the homotransplant. Thus the ability to lower the blood pressure appeared distinct from the ability to excrete common nitrogenous wastes and the ability to concentrate the urine. The return of the hypertensive state corresponded with an obvious deterioration of the kidney.

The reduction of the hypertension could have been mediated by a nonexcretory function or by the excretion of an unknown factor. It seems reasonably certain that the effect did not result from the excretion of common electrolytes of body fluids.

Previous observations (5), confirmed by Kolff, Page, and Corcoran (10), indicated protection against the hypertension when the urine was deviated into the vena cava or small bowel. Kolff and Page (9) also demonstrated a reduction of "renoprival hypertension" by kidney perfusion. These observations tend to support a nonexcretory renal function as operating in the reduction of or protection against the hypertension of nephrectomy, and are in general agreement with the concepts proposed by Grollman (4). Reduction of the postnephrectomy hypertension by a nonexcretory function of the renal homotransplant appears as a plausible explanation for the findings herein presented.

SUMMARY

1. The postnephrectomy hypertension of the dog was significantly lowered for a period of 4 to 5 days following the application of a homogenous renal transplant.

2. The reduction of the postnephrectomy hypertension apparently did not result from the loss of water and sodium from the animal.

3. A preliminary sodium load was not necessary for the reduction of the blood pressure following the renal homotransplant.

4. Observations on autogenous renal transplants as well as certain studies of the homotransplant indicated evidence of renal injury mediated by the transplanting procedure. This injury was reflected by an excretory renal insufficiency which did not prevent the ameliorative influence of the renal homotransplant on the hypertension following nephrectomy.

5. The renal homotransplant apparently was able to overcome the aggravating influence of dietary protein on the hypertension following nephrectomy.

6. The transplanting operation per se was not responsible for the reduction of the hypertension as indicated by failure of a sham operation to lower the blood pressure.

7. A suggestion of protection of the vascular system against the injury of nephrectomy by the renal homotransplant was gained.

8. Renal homotransplants may be useful in attempting to elucidate the function of the kidney which ameliorates the hypertension following nephrectomy. It appears more likely that this function is nonexcretory.

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A STUDY OF THE EFFECT OF RELAXIN ON CONTRACTILITY OF THE NONPREGNANT UTERUS BY INTERNAL TOCOMETRY

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STUDY OF MOTILITY of the human uterus has been in process since 1872 when Schatz contributed his first reports. Subsequent workers have supplied important information with both external and internal hysterography, much of it concerning the pregnant uterus and labor.

Research on contractility of the nonpregnant uterus involves use of internal tocography, and Heinricius in 1889 was the first of the investigators in this sphere. Workers have used many different techniques including balloons, bags, catheters, hysterosalpingographic contrast media, microcarbon electroreceptors and intrauterine electrodes. The contributions of Karlson (11) with his microcarbon electroreceptors have been especially important; his method is superior to other methods because it is sensitive, has quick reactivity, has no uterine-distending drawback as noted in bag techniques, and offers multiple point tocometry.

The early workers in the study of nonpregnant uterus activity presented evidence of motility during the normal menstrual cycle similar to that observed in animals. Knaus reported that during the first half of the menstrual cycle the human uterus showed rhythmic spontaneous motility with frequent contractions of low amplitude, and that in the latter half of the cycle there was quiescence and no activity. He attributed this decrease in activity to the progesterone liberated at the time of ovulation. Wittenbeck and later Palmer and associates reported similar findings. In 1937 Dickinson seemed to confirm Knaus' results; he palpated human uteri through several successive cycles and asserted that there was a distinct pattern of uterine activity reaching its most vigorous state as the follicle matures, subsiding to quiesence as the corpus luteum forms and developing moderate contractility just before and during menstruation.

However, these early reports have not been confirmed by later investigators, especially as far as inactivity during the luteal phase is concerned. In separate studies, 8 different groups have observed definitive uterine motility throughout the menstrual cycle: during the follicular phase the uterine contractions were of small amplitude, high frequency, and high tonus; and in the luteal phase, the contractions were of larger amplitude, less frequency, and there was little or no tonus; in anovulatory cycles, only contractions characteristic of the follicular phase were found.

Doubt concerning the validity of the findings of these numerous investigators was expressed by Reynolds (19). He asserted that animal studies supported Knaus' work in humans and the theory that progesterone had an inhibiting effect on uterine activity, and he stressed Dickinson's palpatory findings in women as important confirmatory evidence. Our results confirm the findings of the previous workers who could not corroborate all of Knaus' early reports and who opposed the assertion that progesterone had a motility reducing property in human uteri.

In the study of the normal menstrual cycle much attention has been focused on uterine motility in cases of dysmenorrhea. During painful menstruation Moir (14),

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Woodbury and co-workers, Wilson and Kurzrok, and Bickers all noted marked myometrial activity with contractions of extreme intensity and duration. These findings further stimulated laboratory and clinical research in the quest for an effective drug to control uterine contractions and thereby modify or relieve dysmenorrhea.

After animal experiments by Reynolds and Allen in 1932 and Morgan in 1935 had shown that corpus luteum extracts had the ability to decrease uterine motility, later studies in 1935 by Allen and Reynolds suggested that it was the progesterone in the corpus luteum extracts which possessed this motility-inhibiting property. This finding led to the treatment of dysmenorrhea with progesterone. Experience has shown progesterone to be of little or no value in therapy of dysmenorrhea, confirming the tocometric studies of the "anti-Knaus school."

Since progesterone was evidently not the factor in corpus luteum extracts responsible for motility-inhibition, investigation turned to that fraction of corpus luteum extract which Hisaw isolated in 1926 and later named relaxin (5); many workers have studied this hormone since then, and the background of relaxin research and assay were reviewed by Hisaw and Zarrow in 1950. A complete review of the biochemical literature on this substance was done by Frieden and Hisaw in 1953.

Animal experimentation with relaxin-containing preparations in purified forms has revealed that it possesses the definite property of inhibition of uterine motility.

Initial clinical investigation with preparations of this hormone to determine its efficacy in relaxing the human uterus and relieving dysmenorrhea was done by Rezek; in 1953 he reported 70 per cent good results in 298 patients with dysmenorrhea. In the same year, Jones and Smith reported similar favorable findings in 67 per cent of 90 women. Eichner and associates in 1956 found salutary effects with relaxin in 3 of 5 patients with painful menstruation. None of these clinical studies, however, had control series, nor did they tocometrically confirm the presumed ability of relaxin to decrease and inhibit human uterine motility. Thus, in an effort to evaluate the uterine relaxing properties of this hormone more objectively, we have investigated a group of normal women in different times of the menstrual cycle, employing the internal tocometric method of Karlson for recording uterine contractions and the effects of relaxin on them.

METHOD OF TOCOMETRY

The hysterographic technique used was described in detail by Karlson (11). Briefly, it is comprised of microcarbon electroreceptors and a recording apparatus. To a steel wire probe, 25 centimeters in length and 1 millimeter in diameter, are soldered 3 receptor chambers (each containing carbon powder) each measuring 12 millimeters in length and 4.5 millimeters in diameter, which are positioned on the probe so that when the instrument is inserted into the normal nonpregnant uterus, 1 each will be located at the fundus, isthmus, and cervix, respectively. From each carbon chamber 2 insulated conducting wires pass along the probe to their respective electrical terminals at the other end (Fig. 1). As the intrauterine pressure increases during a contraction it produces a decrease in the electrical resistance of the carbon causing an increase in the current passing from batteries to 3 self-recording milliammeters (1 each for current from its respective carbon receptor chamber) which are attached to an ink recording system. Opposite effects occur when the pressure decreases as the contraction finishes.

This method is sensitive, efficient, possesses quick reactivity, and permits excellent qualitative portrayal of myometrial contractility in various parts of the same uterus. Quantitative determinations of pressure by comparing milliamperes of current to millimeters of mercury are possible with a special calibrating apparatus, but they are estimations and not precise, though they may be used for comparison with the pressure values obtained in other tocometric techniques

MATERIAL

For purposes of accuracy in this study only women with definite histories of regular menses every 27 to 30 days were selected. Fifty women who had essentially normal pelvic findings and who agreed to co-operate in this study were investigated. These patients had been admitted to the Allmänna Barnbördshuset (The General Maternity Hospital of Stockholm) for various reasons such as dysmenorrhea, sterility work-up, cervical polyp, Bartholin cyst, and leucorrhea. None of the patients studied had had any hormonal medication in the month prior to study. Menstrual histories were as exact as could be obtained, but for more scientific accuracy over 80 per cent of the patients had a dilatation and curettage or endometrial biopsy within 24 hours after the recording to obtain histologic confirmation of the precise time of the cycle; the endometrial specimens were dated histologically according to the criteria introduced by Noyes, Hertig, and Rock.

The patients' ages ranged from 17 to 42; 29 nulligravid and 21 multiparous women were studied.

Twenty-three patients were studied during the first 2 weeks of their cycle—proliferative phase; 19 women were recorded during the 10 days prior to their expected menstruation—secretory phase; and 8 women were observed during their menses. However, 5 of the women thought to be in their secretory phase were later discovered by motility pattern and biopsy to be either in the late proliferative phase or in an anovulatory cycle.

TECHNIQUE

After the patient voided, a careful pelvic examination was performed. If no abnormalities were found, a speculum was inserted into the vagina, the cervix was grasped with a tenaculum, and the uterine depth and direction were determined with a sound. If necessary, a small Hegar sound was used to dilate the internal os slightly (to approximately 4 millimeters) to allow entrance of the sterilized, calibrated receptor probe which was then passed gently upward until the graduated scale on the receptor probe indicated that the carbon chambers were in position in the fundus, isthmus, and cervix, respectively. The electrical connections were then snapped onto the receptor probe terminals and the recording begun. The patient was placed in the supine position where she remained lying quietly for the remainder of the study, a period of at least 2 hours.

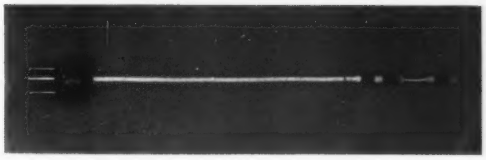

FIG. 1. Receptor probe.

No premedication, analgesia, or anesthesia was ever necessary for this simple procedure. No complications were ever encountered from the use of this technique of tocometry. No uteri were perforated, no bleeding was induced, and no infections developed from these intrauterine investigations.

RELAXIN: ROUTE, DOSAGE, AND TOXICITY

The relaxin used in this study was supplied as releasin®. Its activity is expressed in terms of milligrams of relaxin reference standard—1 milligram of which assayed approximately 150 guinea pig units. (Recently a change to a more pubic ligament assay has been approved by the F. D. A.) The relaxin was furnished in 2 cubic centimeter vials, each cubic centimeter containing activity equivalent to 20 milligrams of the standard —or 3,000 guinea pig units per cubic centimeter.

For purposes of exact timing of onset and duration of effect of relaxin, we employed the directly intravenous route of administration. The dosages varied from 0.5 to 14.0 cubic centimeters in attempts to obtain optimal results; the average initial dose was 2.0 cubic centimeters and the average total amount of relaxin given to each patient was 10.0 cubic centimeters.

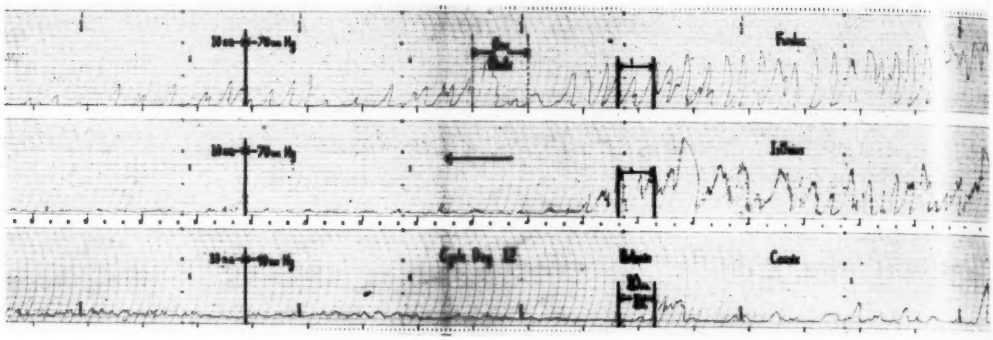

FIG. 2. Cycle day 12: effect of relaxin on P.P.P.

Previous reports have found no antigenicity, sensitivity, or toxicity to relaxin; 1 patient was reported as having developed chills during the administration of relaxin intravenously via a glucose and water infusion, but it was thought that the chills were more likely due to the vehicular solution.

In this series of 50 patients, we encountered 5 instances of development of chills shortly after administration of the relaxin; in each case the patient had received an initial dose of intravenous relaxin 10 to 30 minutes previously, suggesting the development of sensitivity in these patients. The chills were transient and were associated with no urticaria or other symptoms. No other side effects or manifestations of toxicity were noted in any of the other patients in this series.

FINDINGS : PROLIFERATIVE PHASE

As mentioned previously, there were 23 patients studied in this group; however, the 5 women, thought to be in the secretory phase who were later discovered actually to be in the proliferative phase, will be analyzed together with the others, making a total of 28 cases in the estrogenic stage of the cycle.

Tocometric recordings revealed the same general pattern of uterine contractility in all the patients in this group. These deflections, we shall refer to as the proliferative phase pattern—P.P.P. (Moir [15] has called this the A-wave pattern.) It is characterized by moderate tonus in the fundus and isthmus, with superimposed contractions of small amplitude and high frequency, usually synchronous in fundus and isthmus; cervical motility is generally confined to small, irregular contractions with no recognizable order. The P.P.P. was observed in each case for approximately 1 hour, and then the relaxin was given in the dosages already described.

In 24 of the 28 patients there was an immediate reduction in uterine motility after the initial dose of intravenous relaxin (Fig. 2); 15 of the 24 cases in a short time had complete abolition of motility, while the other 9 had only low grade activity. In both instances the inhibition of contractility persisted for a period of 40 to 60 minutes depending on the amount of the initial dose; at the end of this time the P.P.P. gradually reappeared with its characteristics intact. At this time repeated dosages of relaxin, in increasing amounts, had rapidly decreasing motility-reducing powers and always shorter durations of effect, as the uterus developed tolerance to the drug. Usually administration of the third dose after the initial one, produced absolutely no change in the contractility pattern.

The 4 patients on whom relaxin had no effect were all studied at approximately ovulation time; biopsies of the endometrium revealed 16 to 18 day endometrium in 3 cases; however, no biopsy was done in the fourth case.

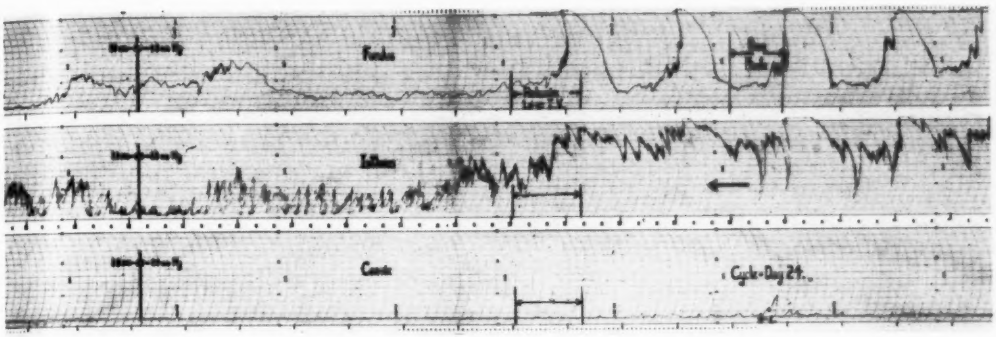

FIG. 3. Cycle day 24: effect of relaxin on S.P.P.

FINDINGS : SECRETORY PHASE

Minus the 5 patients who were found actually to be in the proliferative stage, there were then 14 women recorded whose motility patterns and endometrial biopsies both revealed evidence that they were in the luteal phase.

Tocometric tracings exhibited the same general pattern of uterine contractility in all the patients in this group. These curves, we shall refer to as the secretory phase pattern—S.P.P. (Moir [15] has called this the B-wave pattern.) It is characterized by synchronous contractions in the fundus and isthmus of large amplitude, and relatively low frequency (1 every 2 to 3 minutes, with a duration of approximately 60 seconds). Tonus was usually slight or absent, although it was occasionally moderate in the isthmus; the cervix was generally inactive. The S.P.P. was observed in each case for approximately 1 hour, and then relaxin was given in the doses already described.

In 8 of the 14 patients there was an immediate reduction in the contractions of the S.P.P. after the initial dose of intravenous relaxin (Fig. 3); 3 of these 8 patients had complete cessation of motility, and the other 5 had a marked inhibition of frequency, amplitude, and duration of contractions. In all 8 cases the relaxative effect lasted approximately 1 hour depending on the size of the initial dose. Upon return of contractility (the typical and characteristic S.P.P. resumed in every case), subsequent administrations of relaxin, even in increasing amounts had less effect as the uterus developed tolerance rapidly.

The S.P.P. of the other 6 patients was very slightly or not at all affected by relaxin, even in very large doses, repeatedly.

FINDINGS : DYSMENORRHEA

There were 8 patients recorded during a painful menstrual period; each of these patients was in the early twenties, had never been pregnant, and had had severe essential dysmenorrhea for several years.

Each patient was studied on the first to third days of menstruation, and the tocometric recordings were noted to exhibit the same general contractility pattern in each case. The typical pattern was characterized by fundal contractions of large amplitude and fair duration, which were usually exactly coincident with the severe cramp-like menstrual pains as experienced by the patient. Surprising findings were the nearly complete absence of isthmal activity and the lack of either fundal or isthmal tonus in all of the patients studied. The cervix, on the other hand, exhibited a high degree of tonus in most cases, with small superimposed contractions of high frequency. Each of these patterns was observed for approximately 30 minutes, and then relaxin was given in the doses already described.

In 7 of the 8 patients studied there was a marked reduction in amplitude, frequency, and duration of contractions immediately

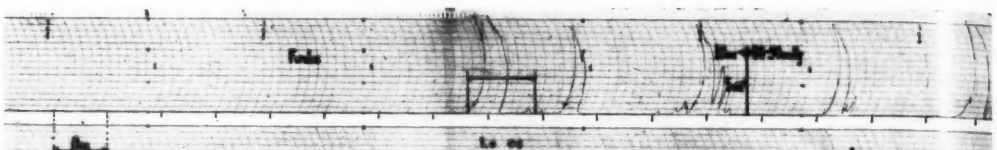

FIG. 4. Cycle and menses day 3: effect of relaxin on M.P.P.

following the initial intravenous injection of relaxin (Fig. 4). In 4 patients tocometry revealed complete cessation of all uterine activity whereas in the other 3 cases motility was greatly reduced but not obliterated. All 7 patients had definite relief of pain coincident with diminishment of contractions on the tocometric tracing, and similarly when the recordings revealed beginning resumption of the typical menstrual contractility pattern approximately 1 hour later, each patient would begin voluntarily to voice her complaints about the return of pain. Repeated injections of relaxin were sharply decreased in effectiveness from the initial injections when given in attempts to inhibit the resumed motility; likewise, the duration of effect was shorter with each successive injection, so that usually there was no effect with the third injection of relaxin.

In 1 patient administration of relaxin produced only slight effect in reducing the contractions and this effect was transient, lasting only 5 minutes; repeated, larger doses of relaxin had no effect at all. At no time did the patient experience any relief from her menstrual pains.

DISCUSSION AND CONCLUSIONS

Analysis of the tocometric recordings of the uterine motility of 42 women in either the follicular or luteal stages of the normal menstrual cycle have confirmed the assertions that there are two definitive contractility patterns : one in the proliferative phase, presumably under estrogenic control, and the other in the secretory phase, probably under progesteronic influence. Studies with the tocometer of 8 patients during a dysmenorrheic period have revealed a particular myometrial contractility pattern. Unquestionably, the changing ovarian hormonal interrelationships are the explanation for these varying facets of uterine physiology.

We have observed that the hormone relaxin is very effective in allaying uterine motility in a large majority of patients in the proliferative phase of the menstrual cycle and also during painful menstruation; the drug is much less effective in women who are in the secretory phase.

Caution must be used in drawing conclusions from these results, since the number of cases studied is too small to be statistically significant and because the hysterographic observations were obtained under the artificial conditions (with their inevitable amount of uterine irritation, however small) necessary in the performance of intrauterine tocometry.

However, from the findings presented it seems that the motility-reducing effects of relaxin are most potent and pronounced in the follicular part of the cycle or during menstruation, when the corpus luteum (and its progesterone) is absent. Why is relaxin so much less effective on the "progesterone-controlled" uterus?

For years it has been known that the best results with relaxin in experimental animals

have been obtained on estrogen-primed subjects, especially in regard to relaxation of the symphysis. One possibility might be that the same estrogen-priming is a requisite for relaxin control of myometrial activity; that the decreased effectiveness and ineffectivity of relaxin in the secretory phase is due to the "neutralization" of estrogen by progesterone, with resultant removal of the "estrogen-trigger" necessary for the effective action of relaxin. Another possibility is that the progesterone of the corpus luteum, itself, neutralizes relaxin directly, thereby inhibiting its effect during the secretory phase.

However, these premises do not explain why some patients in the secretory phase show good effects on reduction of motility following treatment with relaxin. Perhaps a more plausible explanation lies in the possible varying amounts of endogenous relaxin produced by the individual corpus luteum; when the combination of endogenous and exogenous relaxin is of such an amount that they overbalance the endogenous progesterone, then the inhibition of motility occurs as in the proliferative phase and dysmenorrheic patients, but, when there is insufficient endogenous relaxin produced by the corpus luteum, then exogenous relaxin alone is not sufficient to overcome the progesterone-controlled uterine activity. This latter theory of endogenous relaxin being the key factor would also explain dysmenorrhea to some extent: a woman whose corpus luteum produces an insufficient amount of endogenous relaxin will have intense, painful uterine contractions; furthermore, these contractions can be definitely relieved by the administration of exogenous relaxin—although only temporarily. The relatively rapid development of uterine tolerance to commercial preparations of the hormone relaxin is a physiologic manifestation of smooth muscle which is true for many other drugs also.

There is much work to be done in the investigation of these complex problems of myometrial motility, and clinical research is doubtlessly only on the threshold of knowledge in this field. We have presented this report in the hope that the tocometric study of the hormone relaxin with its effect on uterine contractility in various stages of the normal menstrual cycle has contributed information which will be of help in the ultimate complete solution of the fascinating mysteries of uterine physiology.

SUMMARY

1. Tocometric study of the effect of the hormone relaxin in reducing uterine contractility has been accomplished on 50 women in various stages of the normal menstrual cycle.

2. The tocometric technique employed was the intrauterine, electrohysterographic method of Karlson using microcarbon receptors in the fundus, isthmus, and cervix.

3. Typical definitive patterns of contractility have been described for the proliferative and secretory phases of the cycle; characteristics of the tracings of myometrial motility in dysmenorrheic patients have been presented.

4. Relaxin has been shown to possess strong motility-inhibiting properties in the vast majority of cases studied in the proliferative phase and also in dysmenorrheic patients; it was found to be definitely less effective in the secretory phase.

5. Discussion of the hormonal control of uterine motility has been presented, and possible explanations for the decreased effectiveness of relaxin during the secretory phase have been advanced.

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A CLINICAL STUDY OF PULMONARY EMBOLISM

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VIRCHOW established the relationship of phlebitis of the lower extremities to pulmonary embolism in the period between 1846 and 1856. Since that time pulmonary embolism has come to be recognized as one of the most dreaded postoperative complications. In spite of the attention focused upon it, the advent of antibiotics, early postoperative ambulation of patients, the routine administration of anticoagulant drugs in subtherapeutic doses, prophylactic ligation of the superficial femoral veins, the wearing of elastic stockings by bedridden patients, and other preventative measures, there has been no significant decrease in the incidence of this phenomenon.

Most clinicians have been faced suddenly with an acutely ill patient who, a few minutes before, was doing well. Some of these patients may die abruptly, while others may survive the initial pulmonary embolus to have repeated emboli or to recover without further difficulty. As with any disease of uncertain etiology, therapy has been empiric, results varied, and statistics difficult to evaluate.

CLINICAL DATA

During the past 6½ years, we have seen in consultation all cases of venous thrombosis and pulmonary embolism on the surgical, gynecologic, and obstetric services at Duke Hospital. During this time, 357 cases of deep venous thrombosis and 60 cases of pulmonary embolism have been treated and followed.

The youngest person among these 35 males and 25 females was 19 years old and the oldest was 77. The average age of the 60 patients was 47.4 years. Twenty-one were overweight and 3 were underweight; race distribution paralleled that of hospital admissions. Twenty-eight were on general surgery and the others fairly equally distributed among the surgical specialties, gynecology, and obstetrics. Forty-seven patients had single emboli, 13 had multiple emboli. Thirty-eight emboli occurred postoperatively, 2 associated with malignancy, 7 associated with trauma, and 13 were idiopathic in origin. Three of these emboli were fatal, 2 being fatal with the initial episode. There were 5 cases of embolism which occurred while the patient was on anticoagulant therapy and 1 after medication was stopped; these will be discussed. Thirty (50 per cent) of these patients had emboli without any physical signs of peripheral venous thrombosis; it is assumed that these emboli arose from the pelvis. Nine patients had signs of venous thrombosis in the right lower extremity and 11 in the left; 10 patients had bilateral venous thrombosis. The following symptoms were experienced by this group of patients: none in 30 patients, calf tenderness in 20, leg pain in 16, Homans' sign in 12, leg swelling in 9, groin tenderness in 8, and pretibial vein dilatation in 1. Our experience has been similar to others in that the majority of these emboli, 51, lodged in the lower lobes of the lungs. Smith (1) has demonstrated a streaming or layering of the pulmonary blood flow and uses this explanation for the apical location of reinfection tuberculosis and the lower lobe location of emboli from the lower extremities.

The prothrombin level was determined at the time of the initial embolic episode. In 3 cases it was found to be greater than 100 per cent and in 7 under 90 per cent; no clotting time was less than 3 minutes. Twenty-three of these patients were kept

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on anticoagulant therapy for 10 to 15 days and 14 for 3 weeks or longer. There was a tendency to treat these patients longer as the study progressed. The only complication encountered in anticoagulant therapy, other than the recurrences reported later, was bleeding in 7 patients. This was a severe problem in patients following prostatic surgery. Wound bleeding was severe enough to cause disruption in only 1 patient.

Our minimal criteria for the diagnosis of pulmonary embolism were sudden distress referable to the chest without other cause, the auscultation of rales or friction rub previously absent, and "compatible" x-ray changes. Several other patients were suspected of having had a pulmonary embolus and were treated as such; they are not included in this study because of a failure to demonstrate 1 or more of the findings mentioned.

DIAGNOSIS

The frequency with which the diagnosis of pulmonary embolism is made varies directly with the alertness of the physician to its possibility of occurrence. This diagnosis is not an easy one, except in the few cases in which the signs and symptoms are typical. If the patient presents with acute pleuritic pain, dyspnea, hemoptysis, and cough, the diagnosis can be made if it is brought to mind. Often, however, the patient does not present this clear picture and symptoms can vary from none at all to sudden death.

Most patients initially have symptoms referable to the chest, and in our experience they are referred to as either a pain, a catch, a tight feeling, a fullness, an inability to take a deep breath, or a shortness of breath. A few hours later the patient may or may not produce blood streaked sputum. These symptoms may be confused easily with myocardial infarction, angina, gallbladder disease, indigestion, or pneumonia. Often one is taxed to make an accurate diagnosis. In the examination of the patient, we frequently find an elevated pulse rate and localized rales; pleural friction rubs are found rarely as an early sign. The absence of leg signs does not rule out pulmonary embolism; as mentioned before, one-half of these patients had no signs or symptoms of deep venous thrombosis of the lower extremities.

Roentgenograms have been an aid in the early diagnosis of pulmonary embolism but have been seldom, if ever, conclusive. Reports were usually "compatible with" or "suggestive of" pulmonary embolism. This uncertainty may have been partially due to the poor quality of the films since they were obtained with portable equipment at the patient's bedside. Hampton and Castleman, in their correlation of x-ray and autopsy findings, came to the conclusion that there were no x-ray findings which might be said to be typical or diagnostic of pulmonary embolism or infarction.

Electrocardiograms have been useful in ruling out myocardial infarction as a cause of chest pain, but have been of little immediate positive help in the diagnosis of pulmonary embolism. The electrocardiographic pattern of acute cor pulmonale has been evident in about 20 per cent of the 273 patients with this condition reported by Paul D. White (8) and his group.

The conventional laboratory blood studies have been of no use in establishing the diagnosis. As seen in our data, no hypercoagulability state, as measured by prothrombin time or clotting time studies, existed. We do not deny a hypercoagulability state, however, as a possible etiology of venous thrombosis. This theory is now under experimental study in our laboratory.

TREATMENT

It is our present feeling on the surgical service at Duke University Hospital that as soon as signs and symptoms suggest venous thrombosis or pulmonary embolism, the patient should be treated with anticoagulant drugs in the following manner. Base-line clotting and prothrombin times are drawn prior to the administration of any anti-

coagulant drugs. The patient is then given an initial dose of 50 to 75 milligrams of heparin intravenously. The clotting time is maintained between 30 and 45 minutes by subcutaneous heparin given every 4 hours for a minimum of 4 days. The clotting time is checked twice a day at 30 minutes and 3½ hours after 1 of the heparin injections to determine the highest and lowest clotting times between injections. We believe that the additional expense and trouble of giving heparin for these 4 days is justified since its action in blocking the blood clotting mechanism is more specific than that of the coumarins. After 4 days the venous thrombosis is thought to be well enough organized to minimize the danger of its being dislodged; it is at this time that the patient is started on dicumarol each daily dose being given after the determination of the prothrombin level. When the prothrombin level reaches the therapeutic range of 10 to 30 per cent, the heparin is discontinued and the prothrombin level thus maintained for a minimum of 21 days. Absolute bedrest in a modified Trendelenburg position, if it is tolerated, is maintained during the first 4 days. The patient is then gradually ambulated with elastic bandages extending to the knees. Sitting or standing is discouraged; elevation of the feet and walking are encouraged. We have found the accompanying chart (Fig. 1) a great aid in our management of the patient's anticoagulant therapy. A typical course of such therapy is shown. Antibiotics are used routinely to prevent secondary infection in the lungs.

We now think that any patient who is suspected of having had a pulmonary embolus should remain on anticoagulant drugs for at least 21 days. If the patient has signs or symptoms of severe or deep venous thrombosis, therapy is extended for 4 or more weeks depending upon the rapidity of his progress.

Certain contraindications to this mode of therapy are recognized and exist principally when progressive thrombosis or major

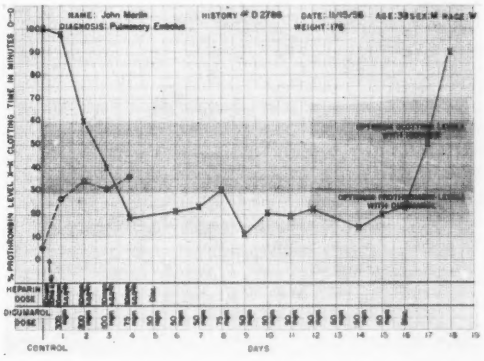

FIG. 1. A typical course of anticoagulant therapy as charted on our anticoagulant charts.

hemorrhage during anticoagulant therapy occurs.

Anticoagulant therapy has been most unsatisfactory following prostatic surgery, and pulmonary embolism following prostate resections should be included among the indications for inferior vena cava ligation. Procrastination in such an instance (see Case 2) probably cost the life of 1 such patient.

Our experience with vena cava ligation has been limited, but we include in our indications for this operation suppurative pelvic thrombophlebitis and the need for protection from pulmonary embolism in the face of progressive thrombosis or major hemorrhage. In many instances, the indication for one mode of therapy and the contraindication for another are relative and in such instances sound surgical judgment should prevail.

RESULTS

Five of our patients experienced pulmonary emboli while on anticoagulant therapy with coumarin. A brief abstract of their cases is presented.

CASE 1. M. G., a 33 year old female with rheumatic heart disease and mitral stenosis, had experienced multiple pulmonary emboli while her prothrombin time ranged between 19 and 29 per cent. Following ligation of the inferior vena cava she had no further emboli and obtained some relief of her congestive heart failure. She later underwent mitral valvulotomy and had no further emboli. Two years after operation her condition is satisfactory.

CASE 2. W. S., a 74 year old male with benign prostatic hypertrophy, underwent a transurethral resection of the prostate. His postoperative course was complicated by pulmonary emboli. He was placed on dicumarol therapy but massive prostatic hemorrhage necessitated termination of this therapy. Repository heparin was started a few days later after the patient had had an increase in temperature and minimal chest signs. The patient died 2 hours later while straining at stool. Prothrombin time at the time of death is unknown but probably was not within therapeutic limits.

CASE 3. M. H., a 42 year old female, underwent a Miles abdominoperineal resection for carcinoma of the rectum. Shortly after operation she had typical findings of pulmonary embolism. She was placed on dicumarol and was given aqueous heparin and repository heparin once. Two days later, with a prothrombin time of 21 per cent, she had a second pulmonary embolism. Following this episode she made an uneventful recovery.

CASE 4. M. S., a 53 year old female with thrombophlebitis, was treated with tromexan. While on this therapy, prothrombin time was difficult to control. She experienced chest pain with typical x-ray findings 4 days later. A prothrombin time drawn immediately was 26 per cent. The patient was placed on heparin therapy and no further emboli occurred.

CASE 5. E. S., a 71 year old colored male with benign prostatic hypertrophy, underwent a retropubic prostatectomy. Seven days following operation, he experienced sharp chest pain and pain on deep inspiration. Examination revealed an elevated pulse rate, tenderness in the left anterior axillary line with dullness in that same area, and a friction rub. X-ray films showed a wedge-shaped density in that area. He was treated with heparin and dicumarol. Hematuria developed the following day with a prothrombin time of 16 per cent, and 10 milligrams of mephyton were given. One week later another pulmonary embolus occurred and the inferior vena cava was ligated. Urine remained clear and no further emboli occurred. Some postoperative edema was controlled with ace bandages when the patient was ambulated and with elevation of legs when he was at rest.

Our experience with these 5 cases caused us to modify our plan of therapy as follows: First, we came to rely on heparin in the early course of thromboembolism rather than on the coumarins. Second, it intensified our belief that pulmonary embolism after prostatic surgery should be treated by inferior vena cava ligation if bleeding recurred with heparin therapy.

These patients have been under follow-up observation for from 6 months to 6 years and with 1 exception there has been no recurrence of the pulmonary embolism following the cessation of therapy. The 1 recurrence was in T. L., a 61 year old male, who was treated with tromexan for 13 days because of venous thrombosis and a pulmonary embolus. Eight days following his discharge from the hospital, he experienced a second pulmonary embolus. He was rehospitalized and treated for a total of 21 days with dicumarol. Since that time he has had no further recurrences.

Fifteen patients have had sequelae from their venous thrombosis, including edema, ulceration, dermatitis, and superficial varicosities. The problem of postphlebitic sequelae is the subject of a current study and will be reported later.

Anticoagulant therapy has been successful in preventing further embolism in 50 of 57 patients initially and with ultimate success in obviating fatal embolism in all but 3. Two patients had to have a ligation of the inferior vena cava. The other patient died during an interruption of therapy due to profuse prostatic bleeding.

DISCUSSION

The most successful therapy for thromboembolism starts with an active program designed to prevent the occurrence of venous thrombosis and thromboembolism. Many schemes have been devised along this line. The early postoperative ambulation of the patient, a step forward, has been augmented by deep breathing exercises, by leg exercises, and by frequent changes of position for those who cannot be ambulated. The wearing of elastic stockings by these patients has been shown by Wilkins and others to increase the velocity of blood flow in leg veins, thus reducing stasis as a possible cause for venous thrombosis. Allen (2) and Miller and Berry have advocated prophylactic postoperative anticoagulant therapy, bicycle exercises, elastic bandages for varicose veins, and forced walking as further preventative measures. Allen (2) also advocated femoral vein interruption if the pa-

tient had a large embolus, if the patient was over 50 years of age, or if there was a danger of a low prothrombin time.

Anlyan (4) and others have reported a high incidence of pulmonary embolism following femoral vein ligation. They observed 5 of 7 patients developing pulmonary embolism in a 2 to 15 day period after vein ligation with 1 fatality. The experience of Ravdin and Kirby, Allen (2), and Roe and Goldthwait at the Massachusetts General Hospital has been of a similar nature.

Postoperative ambulation is encouraged at Duke Hospital. When the patient is not walking, he is encouraged to sit with his legs elevated and not hanging from a chair or from the bedside. Elevation of the foot of the bed is maintained.

As alertness to the possibility of pulmonary embolism is an essential part of one's diagnostic armamentarium, it is well to know when and where to expect this occurrence. Barker and others at the Mayo Clinic tabulated the frequency of pulmonary embolism after 172,888 operations. It was found to occur in 0.52 per cent of all operations, 3.32 per cent of splenectomies, 2.41 per cent of all intestinal resections, 2.17 per cent of all other intestinal operations, and 1.52 per cent of all hysterectomies.

Ochsner (12) reported postoperative emboli in 0.05 per cent of 647,868 operations.

Goyette stated that there is no precipitating cause in the majority of patients but that certain conditions were found to be associated frequently with pulmonary embolism and listed them as follows: (1) a previous history of embolism; (2) extensive varicosities of the legs; (3) congestive heart failure; (4) malignant tumors; (5) extensive pulmonary or abdominal surgery; (6) obesity; (7) patients over 50 years old; (8) extensive trauma to the legs; (9) immobilization; (10) polycythemia vera.

We are in agreement with these situations save the one dealing with cancers. We can find no cause to believe that malignancy per se predisposes one to thromboembolism or venous thrombosis except in the far advanced cases, and there, in no greater incidence than in other chronic debilitating diseases (5).

Allen, Barker, and Hines (3) state that if a patient has a pulmonary embolism after operation and survives, there is a 43.8 per cent chance of another thrombotic episode, a 30.5 per cent chance of another embolism, and an 18.3 per cent chance of a fatal embolism in the same postoperative convalescence.

Three of our patients with idiopathic venous thrombosis besides pulmonary emboli while in the hospital were followed as out patients, and all 3 were noted to be wearing trusses for inguinal hernias. The wearing of a truss had been either overlooked or not elicited in taking their initial histories. In each case the truss was on the side of the venous thrombosis. This pressure over the femoral vein probably played a part in the development of the venous thrombosis. This observation is in support of the theory of stasis as a cause of venous thrombosis.

To point up the frequent difficulty in making a correct diagnosis in pulmonary embolism, Miller and Berry recorded the clinical diagnosis given as the cause of death in their series of 104 fatal cases of infarction. Forty-four were accurately diagnosed; the causes of death in the rest were listed as congestive heart failure, myocardial infarction, pneumonia, bronchogenic carcinoma, cerebrovascular accident, and other conditions. The typical picture of pulmonary infarction was seen in only 15 of the 104 cases. In 14 cases none of the so-called classical findings were present—pleural pain, hemoptysis, dyspnea, or friction rub. Elevated pulse rate and rales were their most frequent findings. Friction rub, probably due to its transient nature, was found in only 9 of these 104 cases.

The absence of leg signs in one-half of our cases at the time of pulmonary embolism parallels the experience of Ochsner and others who state that there was no clinical evidence of an antecedent thrombus in

approximately one-half of their reported series of patients with pulmonary embolism.

As more and more experience is gained with the anticoagulant drugs in the treatment of thromboembolism, there appears to be less and less controversy in the literature as to its preference in therapy. Indications for the ligation of the inferior vena cava are becoming more clear-cut. Payne has written extensively on this operative procedure and has set forth his indications for it. Thebaut and Ward reported 34 cases of vena cava ligation with 2 deaths at the table but no recurrence of pulmonary embolism in the other 32 patients following this procedure. Our experience has been limited but highly satisfactory.

SUMMARY

The clinical experience of the authors with 60 cases of pulmonary emboli is presented. All cases were on the surgical, gynecologic, and obstetric services. Fifty per cent of these pulmonary emboli occurred without any signs or symptoms of venous thrombosis, and 3 emboli resulted in death. All cases were initially treated with anticoagulant drugs; 2 patients, however, required ligation of the inferior vena cava. The difficulty of an accurate diagnosis is stressed and its achievement discussed. A plan of therapy is outlined and case histories of 5 patients who had pulmonary emboli while on anticoagulant therapy are presented. The necessity of ligation of the inferior vena cava in case of pulmonary emboli following prostatic surgery is pointed out.

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INTRALOBAR BRONCHOPULMONARY SEQUESTRATION

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THE THORACIC SURGEON is encountering with greater frequency an anomalous systemic artery associated with sequestrated pulmonary tissue. The vessel arises from the aorta near the diaphragm, traverses the inferior pulmonary ligament to join the lower lobe of the lung at the site of partial or complete developmental separation of a portion of the lung from the normal bronchial tree. The term "intralobar bronchopulmonary sequestration" has been applied to this pulmonary abnormality. While there have been only 94 cases reported in the literature, the fact that most of these cases have been reported during the last 5 years is convincing evidence that this condition occurs more frequently than previously recognized.

We have collected a total of 94 cases from the world literature to which we are adding 6 cases of our own. Clinical and morphologic studies are presented.

INCIDENCE

Cole and his associates, in reviewing 460 thoracotomies, observed 2 cases in which an anomalous vessel communicated with a cystic abnormality of the lung. This is an incidence of 0.4 per cent.

Pryce collected 6 cases of the dual abnormality from 336 pulmonary excisions, an incidence of 1.8 per cent.

Three cases in our series are collected from 385 thoracotomies at Firmin Desloge Hospital during the past 5 years, for an incidence of 0.8 per cent.

CLINICAL FEATURES

The sex incidence of male to female is approximately 3 to 2. The ages at the time of operation ranged from 20 months to 67 years. The clinical picture is generally that of recurrent pneumonic infection often dating back to childhood. Physical findings are often minimal to absent. Occasionally changes in resonance in the lower posterior lung field, with a few moist rales, may be present. The left lower lobe is involved more frequently than the right.

ROENTGENOGRAPHIC FEATURES

The usual appearance of the sequestered lung tissue on a posteroanterior film of the chest is that of chronic infection with single or multiple thin walled cysts, often containing fluid and air, occupying the basal segments of the lower lobe. Occasionally, a zone of consolidation may obscure the cyst. However, the pulmonary ectopia may present as a sharply outlined, rounded or triangular homogeneous mass in the inferior portion of the lower lobe.

Landry and Salatich believe that on the posteroanterior view of the chest the presence of long branching vertical lines directed toward the diaphragm suggests an anomalous vessel and that planeography may be useful for a further demonstration of the artery.

Bronchoscopy is usually normal, although, with infection, exudation from the basal segmental bronchial orifices may be seen. A bronchogram often demonstrates a filling defect or superior displacement of a lower lobe bronchus, but no contrast media enters the cystic structure.

PATHOLOGY

The lower lobe is the site of pulmonary ectopia with one or more basal segments involved. The relatively well localized area of sequestered lung tissue is usually well demarcated from adjacent lung parenchyma. The diseased portion is firm or rubbery.

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On sectioning the resected lobe, the sequestrated portion may present as a single large cyst, multiple small cysts, a rather well localized bronchiectasis or collapsed lung resembling fetal lung tissue which has never aerated. The major bronchi are slightly dilated and branch around the sequestered portion but are not seen to communicate with the involved segment. Pus often exudes from the cut surface. A varying degree of infection is present about the periphery of the ectopic tissue.

One or more large systemic vessels enter the sequestrated segment usually on the medial aspect. Sections through the artery reveal thickening of the media with hypertrophy of the muscle bundles and an abundance of large, thick, uniform elastic fibers.

The microscopic picture within the sequestered lung is a variable one. In some areas dilated bronchioles are lined by pseudostratified columnar epithelium. Elsewhere, irregular dilated cysts lined by columnar or cuboidal epithelium bearing little resemblance to bronchiectasis are seen. An increased number of acute and chronic inflammatory cells and a considerable amount of fibrous tissue scattered through the area are present. The vessels within the diseased portion are large, thick walled, and show advanced atherosclerotic changes.

EMBRYOLOGY

It is generally agreed that this dual anomaly is of congenital origin, occurring within the embryo. A brief review of the normal genesis of the lungs presents a clearer understanding of the developmental abnormality.

In the embryo both epithelial and mesenchymal anlage can be recognized. From the anterior wall of the foregut the epithelial anlagen evaginates as a longitudinal groove. A tracheo-esophageal septum is formed and complete separation effected by fusion of the opposite ends of the evagination. Thus the epithelial anlagen of the lung forms a tubular sac descending ventral to the foregut, communicating only as the larynx at the cranial end. The "blind" caudal end bifurcates into two lung buds which form stem bronchi. Progressive monopodial branching from the two stem bronchi occurs into the right and left thoracic cavities with bilateral mesenchymal anlage producing the perivascular stroma.

Pryce has in some detail considered the various stages which may occur in the genesis of intralobar bronchopulmonary sequestration. Of considerable speculation is whether the mode of origin of the anomalous artery is responsible for the pulmonary ectopia. Anomalous systemic arterial supply to normal pulmonary tissue has been repeatedly demonstrated and reported in the literature as early as 1777. It was not until a century and a half later that Fischer associated a systemic artery with sequestered lung. While the anomalous vessel has been noted to supply adjacent normal lung tissue as well as the sequestered mass, it usually supplies oxygenated blood to the intralobar sequestration only. The inferior pulmonary ligament is usually intimately associated with the vessel.

The "fraction" theory explains the occurrence of sequestered pulmonary tissue of the intralobar type to result from detachment within the embryo of part of the developing lung buds. This may result from deepening of the intralobar fissures.

In attempting to correlate the development of the dual association of the anomalous vessel with the sequestered mass, Pryce suggests that traction by delicate embryonic capillaries may lead to amputation of bulbous tips of the developing bronchial tree, the latter composed of only thin epithelium embedded in mesenchyme. This opinion implies that the anomalous vessel in the embryo is the prior abnormality, with sequestration a complication of this.

However, we favor the concept that sequestration results from "fractioning" of the developing lung bud which subsequently seeks its own blood supply attracting adjacent embryonic blood vessels of systemic origin. This latter concept is supported by

Beneke's observation that ectopic tissue may obtain vascular supply from the vicinity if the malformation occurred early enough in the embryonic development. Hamburger has further clarified this point by transplanting limb buds into a new position within the chick embryo. Not only do these buds develop very remarkably, but they also attract blood vessels from the new location.

ANOMALOUS ARTERY

The role which the aberrant vessel plays in relation to the sequestrated pulmonary tissue as yet is not completely clear. In the 100 cases of the dual abnormality reviewed, the vessel took origin from the thoracic aorta in 87 instances and entered the thoracic cavity from the aorta below the diaphragm in only 13 cases. In 7 instances more than one systemic vessel was encountered. While the origin from the aorta favors a nutritive function of the vessel, earlier histologic studies suggested it to be an elastic structure of the pulmonary artery type. Recently, however, attention to the vessel reveals the histologic structure of the aberrant artery to differ rather strikingly from the pulmonary artery. The wall of the vessel is thicker and contains proportionately more muscle tissue than the pulmonary artery. The elastic fibers in the media are larger, thicker, and more uniform than the shorter, less regular elastic tissue of the pulmonary artery. The smaller vessels within the sequestrated lung are thicker walled than in the adjacent normal parenchyma. This fact may be due to accentuated arteriosclerosis from the elevated intravascular pressure.

Although Pryce has pointed out that the anomalous vessel may distribute oxygenated blood not only to the sequestrated mass but also to the adjacent normal pulmonary tissues, more recent studies support the thesis that the nutritive function is confined just to the sequestered portion of the lung. While Tosatti and Cole have demonstrated anastomoses between the anomalous vessel and the pulmonary artery, this relationship has not been verified in a well studied vinyl acetate cast of the vascular pattern within a resected lobe by Lemmon and his associates. They could demonstrate no communications between branches of the anomalous artery and the pulmonary artery. Injection studies of the vascular structures and roentgenographic visualization in Case 6 revealed the independence of the two arterial systems. Venous drainage, however, was effected through the pulmonary veins as has been noted previously.

Rather prompt branching of the aberrant vessel on gaining access to the pulmonary parenchyma, as noted grossly in these cases and in the majority of those reported previously, was demonstrated by injection of the aberrant vessel with contrast media in Case 6 (see Fig. 1).

The relative paucity and coarseness of the blood vessels in the sequestrated segment would support the concept that the anomalous vessel functions primarily for nutrition and is not part of the oxygenating system.

INFECTION

The role of infection in this condition is still not clear. It appears to occur secondarily within the sequestered lung tissue.

Although communications of the bronchi with the sequestered pulmonary tissue are usually not demonstrated with bronchography, one could surmise that at some time bronchial continuity did exist. This would seem to be the most likely portal for bacteria to enter the sequestered lung. However, the concept that direct invasion of the sequestered tissue by bacteria from pneumonic process in the adjacent normal lung is supported by the presence of infection about the cystic area in many resected specimens. The hematogenous portal of entry, while implicated in one of Pryce's cases, does not seem very likely. Upon once gaining access to the cyst the organisms may well lie dormant for long periods of time between bouts of infection.

FIG. 1. Combined injections of anomalous artery and pulmonary artery show the independence of the two systems.

CASE REPORTS

CASE 1. J. S., a 55 year old white male coal miner, was admitted to the Firmin Desloge Hospital for the first time on January 14, 1955, with a history of frequent colds and recurrent bouts of pneumonia occurring intermittently since 1938. The most recent bout began 3 months prior to entry. For the 2 months before admission to the hospital there was a history of dyspnea, aching pain in the left lower chest region, and a chronic productive cough.

Positive physical findings included a slight decrease in resonance in the left base posteriorly; the remaining lung fields were hyperresonant. There were a few rales in the left base.

Roentgenogram of the chest revealed slight emphysema in the lower portion of both lungs. There was an area of increased density in the lower lung field on the left adjacent to the diaphragm, which seemed to produce extrinsic pressure on the cardia of the stomach.

Repeated white blood counts were normal, but there was a persistent lymphocytosis with 42 to 48 per cent lymphocytes reported. Repeated sputum studies showed no acid fast bacilli. Lymph node biopsy revealed reticular hyperplasia. Bronchoscopy and esophagoscopy were negative. Sputa were negative for acid fast bacteria and malignant cells. Pulmonary function studies were not remarkable.

The patient was explored on February 9, 1955, by a posterolateral thoracotomy approach. Operative findings revealed an aberrant systemic artery arising from the aorta just above the diaphragm, measuring 1 centimeter in diameter, traversing the inferior pulmonary ligament to enter the anteromedial aspect of the right lower lobe. The anteromedial basal segment was markedly atelectatic. A left lower lobectomy was performed. The patient made an uneventful postoperative recovery.

Gross examination of the resected specimen revealed the diseased portion to be firm in consistency, containing no air. The adjoining lung tissue was slightly emphysematous. The firm, collapsed area of lung measured 3 by 9 centimeters. On sectioning the lobe it was seen that the disease was confined to the anteromedial basal segment. This area was sharply demarcated from the rest of the lung parenchyma which was normal. A moderate amount of pus exuded from the involved area. Multiple large cysts with a smooth, glistening lining comprised the major portion of this diseased segment. The largest of the cysts was 4 by 3 centimeters. The other cavities were smaller in size, measuring on the average of 2 to 3 centimeters in diameter. The cysts seemed to communicate with each other. A thick, elastic blood vessel measuring 1 centimeter in diameter entered the area of cystic dilatation.

Microscopic section of the atelectatic portion of the lung revealed that it was heavily infiltrated with acute and chronic inflammatory cells, with fibrosis of the vascular channels. There were only a very few alveoli present. Multiple cystic dilatations were lined with low columnar type epithelium. A large number of blood vessels with thickened muscular walls containing abundant elastic fibers were present. Findings were consistent with cystic bronchiectasis, atelectasis of the sequestered lung, and an organized pneumonia.

Perfusion of the anomalous systemic vessel with colored contrast medium and roentgenographic studies revealed prompt evacuation of the media through the pulmonary venous system, with no evidence of communication of the systemic arterial supply with the pulmonary arterial circulation. The independence of the two circulations was confirmed by combined injection of the pulmonary arterial vessels and the aberrant vessel (Fig. 1). Bronchography through the lower lobe bronchus revealed the absence of any communication of the stem bronchi with the sequestrated mass (Fig. 2).

CASE 2. G. H., a 41 year old white female, was admitted to the hospital on March 13, 1951, with a history of recurrent bouts of pneumonia during the past 2 years. Each episode would last about 1 month. Additional symptoms included hemoptysis, persistent low grade fever, night sweats, malaise, and a mild cough productive of small amounts of yellow-green sputum. There was a strong familial history of tuberculosis.

Positive physical findings included nontoxic nodular goiter. Lungs expanded equally bilaterally. Tactile fremitus was equal. Auscultation revealed coarse, moist rales with expiratory wheezing in the left base. The rest of the examination was negative.

Hemogram was normal. X-ray film of the chest revealed an area of infiltration in the posterior inferior portion of the left lung, in the central portion of which there was cavitation suggestive of abscess formation. The rest of the lung field was clear. Second strength PPD was strongly positive.

Bronchoscopy revealed a considerable amount of mucopurulent sputum exuding from the left lower lobe orifice. The posterobasal segmental orifice of the left lower lobe was red and raw in appearance. There was injection of the left main stem bronchus. Bronchial biopsy was negative. Bronchogram revealed the lower lobe bronchi to be arborizing about the cavity in the medial portion of the left lower lobe but none of the opaque media was seen in the cavity.

The patient was explored through a left posterolateral thoracotomy. The left lower lobe was seen to be adherent to the parietal pleura and anchored to the aorta just above the diaphragm by a systemic artery arising from the aorta measuring 13 millimeters in diameter. There was also a hiatus hernia present. Inspection revealed the artery to enter the posterobasal segment of the left lower lobe. The systemic vessel was divided, and a left lower lobe resection was performed with repair of the hiatus hernia. The patient tolerated the procedure well and was discharged home after an uneventful postoperative course.

On palpation, the resected lobe was crepitant and spongy except over the posterobasal segment where it was very firm. On cut section, the bronchi and bronchioles were dilated and filled with both blood and pus. The posterobasal segment was surrounded by yellow and white parenchyma which, when compressed, exuded a creamy purulent material. The bronchi in this area were tremendously dilated right out to the periphery. The grossly involved segment of the lung seemed to blend with the adjacent normal parenchyma. The anomalous vessel entered the diseased segment.

Microscopic sections through the involved segment revealed large, thick walled bronchi lined by pseudostratified columnar epithelium with a marked inflammatory cell infiltration of the wall. A purulent exudate was present around the bronchi. There was a marked proliferation of fibrous tissue. Alveoli were very scarce in the involved areas. Mild emphysematous changes were present in the adjacent lung as was a slight degree of inflammation.

The aberrant vessel was thick walled with an abundance of elastic tissue within the hypertrophied media. The arteries within the diseased segment were thick walled and showed advanced arteriosclerotic changes with fibrous intimal thickening and subintimal lipophagic clusters.

Guinea pig inoculation failed to reveal any evidence of tuberculosis.

Case 3. C. F., a 31 year old white female, entered the Hirmin Desloge Hospital for the first time on August 7, 1951 with the history of recurrent bouts of "pneumonitis" during the past 2 years. During the past several months she had noted a chronic cough productive of about ½ cupful of foul smelling yellow sputum per day. She had received a prolonged course of antibiotic therapy.

FIG. 2. Bronchogram shows no communication of bronchi with sequestrated tissue.

Physical examination revealed no positive findings. Hemogram was negative.

Chest plate revealed an irregular rounded area of increased density in the posterobasal segment of the left lower lobe, approximately 3 inches in diameter. There was no fluid level seen.

Repeated sputum studies failed to reveal any acid fast bacilli. Patch test and PPD were negative.

Bronchoscopy revealed the left lower orifice to be narrowed to approximately one-half the usual size with pus exuding from the orifice. Bronchial biopsy revealed chronic inflammation.

The patient was explored through a left posterolateral thoracotomy. The left lower lobe was adherent to the parietal pleura. A 1 centimeter vessel arose from the aorta above the diaphragm entering the posterobasal segment of the left lower lobe. The lower part of the lobe was occupied by a fluctuant mass. The superior segment was normal in appearance. A left lower lobe resection was carried out without incident. The patient made an uneventful postoperative recovery.

Examination of the resected lobe revealed that a 7 centimeter cyst containing approximately 75 cubic centimeters of pus occupied the basal portion of the

lobe. The wall was thickened with a surrounding zone of fibrosis. The anomalous vessel coursed around the cyst, giving off branches to it.

Microscopic sections revealed a thick, fibrotic abscess wall infiltrated with lymphocytes, plasma cells, and giant cells. There was increased vascularity in the area. Surrounding lung tissue was compressed by the cystic mass. Bronchi in some sections were markedly dilated, thick walled, and showed an inflammatory reaction in the wall. The cyst was lined with low columnar epithelium. Sections through the vessel showed medial thickening with hypertrophied muscle and considerable elastic tissue in the media.

CASE 4. Z. D., a 50 year old white female, was admitted to the Missouri State Sanitarium on August 15, 1951 with a history of recurring bouts of "virus" pneumonia, the most recent of which had persisted for 6 weeks despite antibiotic therapy.

In 1916 she was confined to bed for 1 year with a clinical diagnosis of tuberculosis.

Physical findings on admission included a thin patient with a pectus excavatum. Chest was clear to percussion and auscultation.

Second strength PPD was positive. No acid fast bacteria were found in the sputa.

Chest plate, stereoscopic views, and lateral laminograms revealed a dense, well defined area in the posterior segment of the left lower lobe measuring 3 to 4 centimeters, containing a central area of rarefaction suggestive of a cavity. The left diaphragm was flattened and the costophrenic angle obstructed. Emphysema to some degree was present in both lower lung fields.

Bronchoscopy revealed a normal tracheobronchial tree. Bronchial smear from the left lower lobe orifice revealed exfoliated cells suspicious of malignancy on Papanicolaou stains.

Thoracotomy on August 29, 1951, revealed the left lower lobe to be adherent to the diaphragm and the lateral chest wall. An anomalous artery measuring 1 centimeter in diameter, arising from the thoracic aorta, traversed the inferior pulmonary ligament and entered the left lower lobe. A left lower lobectomy was carried out without incident.

Gross examination of the resected specimen revealed the lateral and posterior basal segments to be occupied by a large, thin walled cyst. The cyst was filled with a gelatinous, brownish-red material. The 1 centimeter anomalous artery entered the lobe on its diaphragmatic surface and divided into 3 larger branches which tended to encircle the cyst for most of its circumference.

Histologic examination revealed that the cyst was lined with low cuboidal epithelium supported by loose connective tissue. The neighboring alveoli were collapsed. There was moderate infiltration by both acute and chronic inflammatory cells.

CASE 5. C. D., a 20 month old white male infant, was admitted to the Missouri State Sanitarium for the second time on June 26, 1951, with a history of 4 bouts of pneumonia during the preceding 8 months. Physical examination disclosed the infant to be in poor state of nutrition, weighing 20¾ pounds. A moderate cough, bronchial bleeding, wheezing, and crepitant rales were heard over the left lower posterior lung field. X-ray films of the chest, including laminograms, revealed an infiltrative process in the left lower lobe with many ring-like shadows suggestive of cystic disease. Second strength tuberculin skin test was positive. Bronchoscopy was negative on 2 occasions.

On August 15, 1951, the patient was explored through the left chest. A cystic left lower lobe was present with a 6 millimeter systemic artery arising from the thoracic aorta, traversing the inferior pulmonary ligament and entering the lateral basal segment. A left lower lobectomy was carried out.

Gross examination of the resected specimen revealed the superior segment to be normal. All of the basal segments had a spongy consistency, with the medial basal segment being quite firm. Sectioning the lung revealed numerous cysts measuring 1 to 10 millimeters in diameter, containing either clear, yellow fluid or thick, inspissated pus. The aberrant vessel on entering the lateral basal segment immediately branched into 3 vessels which appeared to end after penetrating the lung substance for a short distance.

Histologic sections of the lung revealed many small cystic structures lined by atypical epithelium containing some columnar cells which were ciliated. Within the cysts were groups of cells with polyhedral nuclei and granular cytoplasm. Many of the cysts were filled with pus. Adjacent interstitial pneumonitis was also seen.

CASE 6. E. F., a 20 year old white male, was admitted to the Camp Pendleton Naval Hospital after routine chest plate revealed an area of radiolucency in the posterobasal lung field. A gastrointestinal series demonstrated an esophageal hiatus hernia. He was asymptomatic.

Bronchoscopy was negative. Bronchography revealed bronchiectasis confined to the left lower lobe.

Thoracotomy revealed the presence of a complete pleural symphysis. Operative findings included an aneurysmal dilatation of the descending aorta in addition to the hiatus hernia. There were 2 systemic vessels measuring 8 and 10 millimeters arising from the infradiaphragmatic portion of the aorta entering the posterobasal segment of the left lower lobe. A single large vein drained directly into the inferior vena cava from this segment.

A left lower lobe resection was performed, and the hiatus hernia repaired. The postoperative course was uneventful.

Gross examination of the resected specimen revealed the posterobasal segment to be replaced with multiple small cysts. There was no evidence of infection. Adjacent bronchi were dilated but did not com-

municate with the sequestrated segment. The cysts were lined by low cuboidal epithelium.

DISCUSSION

The 6 cases reported here and those recorded in the literature have certain features in common. A clinical history of recurrent pneumonic infections dating back to childhood is usually elicited. A roentenogram of the chest reveals a cystic or solid area in the basilar segments of the lower lobe, with evidence of infection which does not completely clear with medical therapy.

On exploration of the chest an anomalous systemic artery arising from the aorta near the diaphragm is seen to traverse the inferior pulmonary ligament and enter the posterior basilar portion of the lower lobe, branching soon after penetrating the pulmonary parenchyma to supply a grossly infected cystic area of pulmonary ectopia within the basal segments of a lower lobe.

The anomalous artery is systemic in type, nutritive in function, supplies the sequestrated lung tissue, does not communicate with the pulmonary arterial circulation, and is drained by the pulmonary venous system.

Communication of the bronchial tree with the sequestered portion of the lung is usually not demonstrated.

The increasing frequency with which this dual anomaly is being encountered at operation is merely a reflection of the increasing scope of thoracic surgery for persistent localized inflammatory disease. The paucity of reported cases is not a true index of the frequency of this condition. Reports of 3 fatal exsanguinations, as well as several other distressing though not fatal hemorrhages from anomalous arteries should alert one to the possible presence of such vessels when dividing the inferior pulmonary ligament during resection of the lower lobe for inflammatory disease.

The origin of the anomalous vessels in Case 6 represents the thirteenth recorded instance in which this vessel arises from the aorta below the diaphragm.

SUMMARY AND CONCLUSIONS

A review of the literature and report of 6 cases of "intralobar bronchopulmonary sequestration" are presented.

Clinical and morphologic features are reviewed.

The relation of the anomalous artery to the pulmonary ectopia is discussed.

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THE REPAIR OF THE PHRENOESOPHAGEAL LIGAMENT IN SURGICAL TREATMENT OF HIATAL HERNIA

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THE SURGICAL TREATMENT of hiatal hernia has been described by several, including: Harrington, Allison, Sweet, and Madden. It has become apparent that the principal indication for surgery has been the associated presence of reflux peptic esophagitis, and the complications thereof. In some cases without esophagitis, there has been sufficient pain or regurgitation to warrant surgery. Strangulation of a sliding esophageal hiatal hernia has been described but is not common. Therefore, one of the principal objectives of the treatment of this condition is to prevent regurgitation or reflux of gastric contents into the esophagus.

The reason for this incompetence at the cardioesophageal junction in hiatal hernia has not been well explained. We know that normally the intrinsic musculature operates as a sphincter. This is proved by the fact that regurgitation and esophagitis frequently follow certain plastic procedures or resections at the junction of esophagus and stomach in which the sphincter mechanism is lost. In hiatal hernia, the intrinsic sphincter is intact, but still in a certain number of cases regurgitation occurs.

Allison describes a pinchcock action of the fibers of the right crus of the diaphragm which encircle the esophagus which he believes is the principal sphincter mechanism. Another explanation describes the oblique entry of the esophagus into the stomach and the importance of this as a valve in preventing regurgitation. In herniation, this angle is changed considerably and supposedly interferes with the function of the sphincter mechanism.

Pecora concludes from his studies that the diaphragmatic muscular sling and the inferior esophageal constrictor are synergistic. However, in the case of herniation, the sling acting on the stomach would prevent drainage of the intrathoracic cardia and thus be an antagonist to the constrictor of the esophagus.

Regardless of which concept or theory of reflux is accepted, it is a fact that return of the entire stomach to its normal position below the diaphragm prevents this disturbing situation. Therefore, in the repair, it is necessary to anchor the cardioesophageal junction as securely as possible below the level of the hiatus of the diaphragm. Normally, the phrenoesophageal ligament with the overlying pleura and peritoneum is the anchoring mechanism. In the presence of a sliding hernia at this site, these structures form the anterior and lateral portions of the sac and are stretched out and sometimes thinned out to variable degrees, depending upon the duration and size of the hernia.

In most techniques of repair, that are described in the literature, there are two objectives: (1) to reduce the size of the hiatus, and (2) to reconstruct or repair the phrenoesophageal ligament. Some techniques stress one objective more than the other. In the Harrington method, reliance is placed on a strong repair of the hiatus. In the various transthoracic approaches, most authors describe methods of utilizing the sac, which from a practical anatomic viewpoint is the phrenoesophageal ligament. Allison has particularly stressed the importance of incising the sac circumferentially, and suturing the cuff attached to the esophagus to the underside of the diaphragm to restore the phrenoesophageal ligament. Madden has stated that the cuff could be sutured to the top of the diaphragm with less technical difficulty and accomplish the same result. Sweet has

FIG. 1. Placing of sutures through underside of diaphragm and into inverted hernial sac. Note that sac is not opened or incised.

FIG. 2. Completed suturing of sac to underside of diaphragm about the hiatus. Insert, diagrammatic representation.

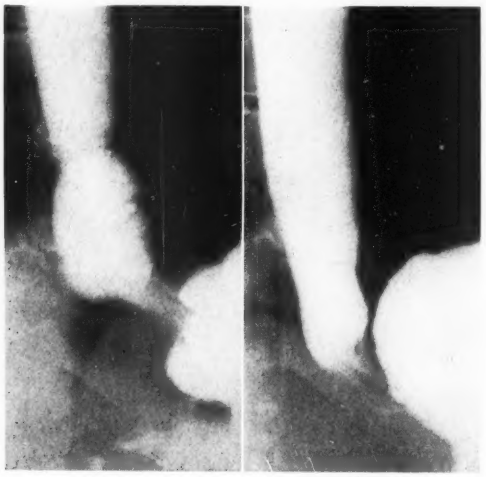
mentioned the plicating of the sac, above the level of the diaphragm. However, in these two latter techniques, the cardioesophageal junction cannot be pulled down as far, nor as well, as it can by employing the Allison method.

If a strong phrenoesophageal ligament can be reconstructed, the repair is more anatomic and physiologic. To rely entirely on reducing the size of the hiatus for a repair omits this important step. Furthermore, the hiatus cannot be closed too tightly about the esophagus or the patient will have dysphagia. Often the crural fibers surrounding the hiatus are thinned out or have to be closed with some tension so that one gets the impression that the sutures may eventually cut through and, in this manner, defeat the purpose for which they were originally placed.

In repairing these hernias, we have favored the transthoracic approach with a small counter incision in the diaphragm to expose the underside of the hiatus, as advocated by Allison. The left phrenic nerve is procainized. The pleura is incised over the lower esophagus as in any of the usual transthoracic approaches. The lower esophagus and hernial sac are mobilized. The extent of the hernia is determined by passing the fingers into the sac from below the diaphragm. Then by traction upon the stomach, the herniated portion is delivered into the abdomen.

To repair the phrenoesophageal ligament, the entire hernial sac is sutured to the underside of the diaphragm. The sac is inverted into the abdomen by placing the index and middle fingers of the left hand into it from above (Fig. 1). The reason that the sac is not opened or incised is that in our experience, once this is done, it often becomes frayed and torn and has insufficient substance to hold sutures. We have observed the carefully prepared cuff described by Allison end up as a few shreds of peritoneum and areolar tissue. The inverted intact sac holds the sutures well, especially when placed through both layers.

The number of sutures depends on the size of the sac. Usually about 3 are placed in the diaphragm at the margin of the hiatus and passed through both layers of the inverted sac. A few more sutures are placed



a b

FIG. 3. a, Preoperative x-ray film of sliding hiatal hernia. b, Same case postoperatively, 1 year after repair by described method.

peripherally (Fig. 2). At the completion of this step of the repair, it will be noted that the cardioesophageal junction is firmly anchored below the level of the hiatus.

It is believed that the procedure just mentioned is just as important in the repair of this defect as the next step; namely, reduction in size of the esophageal hiatus. We prefer to do this by placing Deknatel No. 1 silk sutures through the crural loop on either side, approximating it behind the esophagus. With a Levin tube in place, the hiatus is closed tightly enough to allow the tip of the index finger alongside the esophagus. The diaphragmatic incision is then repaired and the chest closed.

The 5 patients in whom this technique has been used have had immediate and lasting relief of symptoms due to regurgitation and esophagitis. The postoperative x-ray studies have shown entirely satisfactory anatomic and physiologic results. There have been no known recurrences, the longest follow-up being 1½ years. Figure 3 shows an x-ray study of a hiatal hernia in a patient before repair, and the result 1 year after repair by the method described.

CONCLUSION

A method of reconstructing the phrenoesophageal ligament utilizing the intact sac in repair of hiatal hernia is presented. The importance of this procedure in preventing reflux esophagitis is stressed.

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AN EVALUATION OF CECAL SIZE IN IMPENDING PERFORATION OF THE CECUM

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PERFORATION OF THE CECUM in large bowel obstruction has carried an almost fatal prognosis. Two-thirds to three-fourths of the patients can be expected to die very shortly after this catastrophic event. This prognosis has persisted despite every surgical and medical advance in the therapy applied. The explanations for this failure have been concerned chiefly with acknowledging the poor risk represented by these patients who, generally, are old and who usually experience so insidious an onset of obstruction and distention that a misdiagnosis is often made. An absence of accurate criteria to suggest a diagnostic concept such as impending perforation of the cecum has contributed to this unfortunate situation. If a diagnosis could be satisfactorily established before perforation occurs, immediate and appropriate surgery might be expected to lower the mortality rate considerably. It is the purpose of this article to describe and evaluate roentgenologic signs which would warn of impending perforation of the cecum and form a consistent pattern for prediction and judgment.

The problem was first approached indirectly in 1880 when Heschl called attention to the rupture of a segment of bowel which had not been diseased but had been subjected to distention because of an obstruction located at some distal point. He applied the term "diastatic rupture" to describe, inclusively, the stages in the pathology of perforation. He found that over an unknown period of time, a distended cecum would show first a splitting of the taenia. This would be followed in unvarying succession by tears through the outer muscle wall and the inner muscle wall. The mucosa was preserved always as the last barrier. Among the 79 cases subsequently described as "diastatic perforation of the cecum," several demonstrated only a single stage in the process. In a strict sense the cases in which the mucosa had remained intact did not exhibit complete perforation. Emphasis upon this distinction raised practical questions whose clinical implications provided the focus for this paper. If there were distinct, intermediate, stages along the dynamic process to perforation, it would be possible to distinguish clinically a state of impending perforation from actual perforation and it should be possible to measure a critical size of the cecum. Distention of the cecum beyond this critical measurement would then suggest the probability of imminent perforation.

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MATERIAL

The present study was based upon an analysis of the 79 case histories described in the literature, personal experience with 19 cases followed to surgery or postmortem, and an experimental appraisal in 100 patients of the limits to which the cecum might be distended artificially.

DATA: CLINICAL AND EXPERIMENTAL

The 19 patients in this series were similar to the cases reported in the literature. In both groups the clinical manifestations of obstruction were deceptive and often the diagnosis had to await roentgenographic delineation. The history, physical findings, temperature, and white count, as a rule, were found to be unreliable barometers for the presence of perforation. Carcinoma of the left half of the colon was responsible as the primary lesion, in most cases, for the cecal distention.

TABLE I.—PATIENTS WITH CECAL PERFORATION

Patient	*Age, years*	*Greatest transverse diameter of cecum, cm.*	*Primary lesions*	*Procedure*	*Aftermath of hospitalization*
1	81	9.2	Ca of rectosigmoid	Cecostomy	Recovered
2	84	9.7	Volvulus sigmoid	Cecostomy	Expired
3	29	9.8	Carcinomatosis 1° adrenal	Glass rod cecostomy	Expired
4	50	11	Ca sigmoid	Cecostomy	Expired
5	82	11	Ca splenic flexure	Cecostomy	Recovered
6	82	12.5	Incarcerated femoral hernia	Cecostomy	Expired
7	79	13	Ca hepatic flexure	Transverse colostomy	Expired

TABLE II.—PATIENTS WITH IMPENDING PERFORATION OF CECUM

Patient	*Age, years*	*Greatest transverse diameter of cecum, cm.*	*Primary lesion*	*Procedure*	*Aftermath of hospitalization*
1	70	9.0	Ca of rectosigmoid	Cecostomy	Recovered
2	74	9.0	Ca sigmoid	Cecostomy	Recovered
3	73	9.5	Volvulus sigmoid	Reduced at surgery	Recovered
4	72	9.5	Ca transverse colon	Double-barreled colostomy	Recovered
5	49	9.6	Ca sigmoid	Cecostomy	Recovered
6	34	10.1	Volvulus of sigmoid	Reduced at surgery	Recovered
7	64	11.3	Ca splenic flexure	Cecostomy	Recovered
8	81	11.5	Ca rectosigmoid	Cecostomy	Recovered
9	76	12.0	Ca descending colon	Cecostomy	Recovered
10	87	12.5	Ca splenic flexure	Cecostomy	Expired*
11	76	14.2	Ca transverse colon	Cecostomy	Recovered
12	68	16.3	Diverticulitis	Cecostomy	Recovered

*On 53rd hospital day with extensive metastases.

The morbidity and mortality of the two groups differed. Seven patients of the 19 in the present series (Table I) had perforation of the cecum extending through the mucosal layer. Twelve (Table II) displayed no evidence of complete perforation or peritonitis at surgery despite the presence, in several instances, of tears involving the taenia. In the present group, the ratio of cases of impending perforation to actual rupture was almost 2 to 1. This observation is the reverse of what has previously been experienced. In only 6 of the 79 cases, previously reported, had perforation not been complete—a ratio approximating 13 cases of rupture to 1 of impending perforation. This difference, in all likelihood, reflects the encouragement given to immediate surgery when the diagnosis of impending perforation was made in the present series. It is reasonable to postulate that delay increases the chances of through and through rupture though actually it is not known if a critical period of time has to elapse before perforation will occur. In none of the 79 cases reviewed from the literature was the concept of impending perforation used as a diagnosis before death.

The lack of delay before surgery appears to be directly related also to the differences in mortality rates. In each of the 79 cases reviewed, the patient had died soon after hospitalization. There was 1 death among the 12 cases presented here without perforation. It occurred after progressive deterioration over a 53 day period following cecostomy and no immediate cause of death was elicited by postmortem examination. This mortality rate of 8 per cent in impending perforation compares favorably with the rate of 71 per cent in the 7 patients with perforation (5 deaths). The rate of 71 per cent is itself consistent with that of many authors as the mortality in perforation in spite of varied therapeutic approaches. The reduction in mortality is based on a consideration of only 19 cases. However, the difference in mortality is striking when the cases are divided into two categories distinguished principally by the integrity of the mucosal barrier, i.e. perforation versus nonperforation.

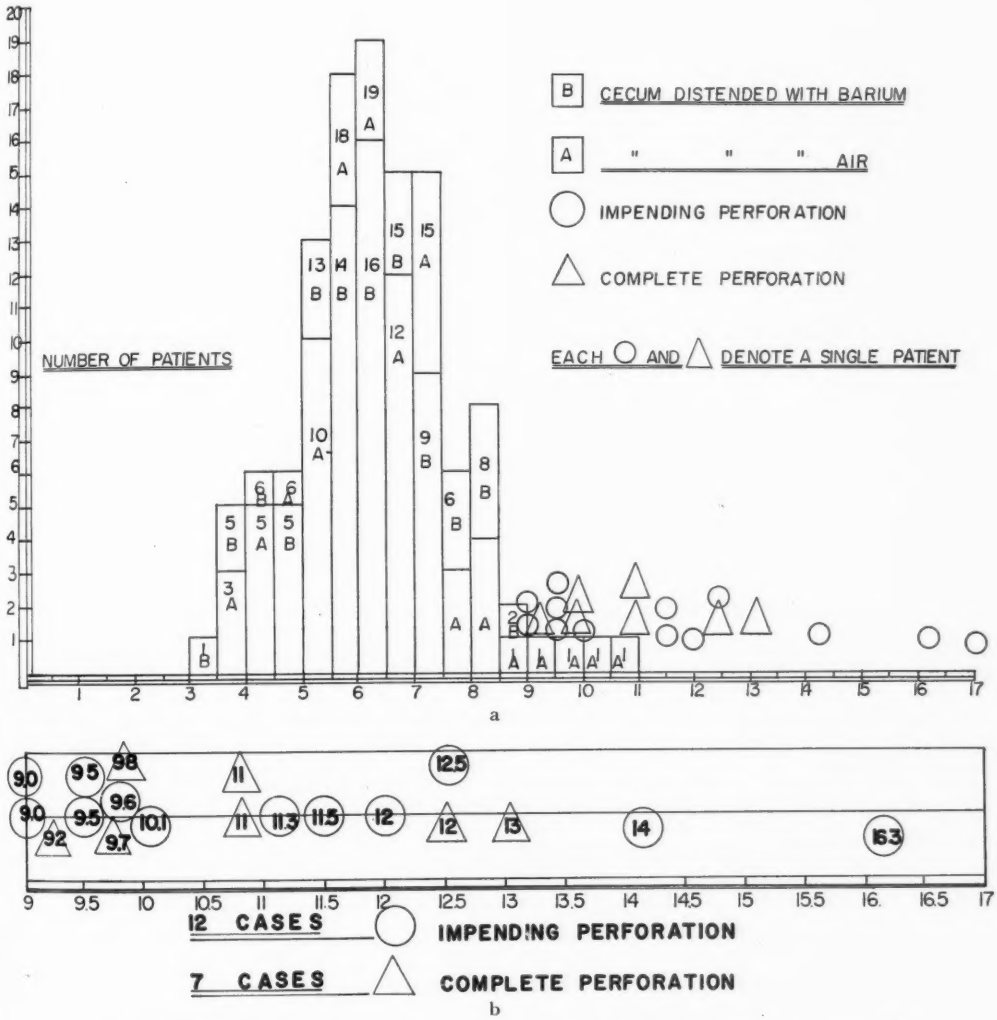

FIG. 1. a, The range of size of greatest transverse diameter of the cecum measured on a prone film in 100 patients distended with barium and with air during the course of barium enema study. The patients studied had no intrinsic disease of the cecum or large bowel obstruction. The size in the greatest proportion of patients fell between 5 and 7 centimeters. b, An enlargement of a portion of graph a. The figures within represent the size of cecal distention. This is a graphic illustration of the abnormal range of cecal distention found in the 19 patients with impending perforation and complete perforation of the cecum.

Roentgen examination offered the most sensitive method for classifying distention of the cecum. Before it could be used, however, it was necessary to investigate the range of size that a cecum might show in the absence of any form of intrinsic distal large bowel obstruction. Since it would be the upper limits of cecal size that would be of primary interest, 100 cases were selected in which the cecum had been distended artificially by barium and by air during the course of barium enema study. None in this control group

FIG. 2.

FIG. 3.

FIG. 2. Male, aged 81 years, greatest transverse diameter of cecum measured 9.2 centimeters. The absence of definition of the properitoneal fat shadows was noted. The linear translucent shadows overlying the cecum suggested escape of air into the paracecal tissues. Operation, November 28, 1949, revealed splitting of the serosa and muscle layers in a localized area of the cecum with free fluid in peritoneal cavity. Cecostomy was done. An obstructing adenocarcinoma of the rectosigmoid was resected later. Patient discharged on forty-seventh hospital day.

FIG. 3. M. T., female, aged 82 years. Greatest transverse diameter of cecum measured 11 centimeters. Loss of definition of the psoas margins and properitoneal fat shadows was associated with the cecal distention. A rectal tube was inserted to outline the course of the rectosigmoid. The findings were interpreted as consistent with perforation. The density in the pelvic cavity was a calcified uterine myoma. At operation on May 29, 1954, a 2 millimeter perforation of the cecum was described with an 8 centimeter fibrin seal. A pericecal abscess was present with free fluid in the peritoneal cavity. Cecostomy was done. Resection of a fungating adenocarcinoma of the splenic flexure was performed at a later date (June 16, 1954). The patient was discharged to home on July 5.

had any form of large bowel obstruction or intrinsic disease of the cecum. In each the greatest transverse diameter of the cecum under distention with barium and with air was measured on a prone film. The 200 measurements were plotted on a graph and compared with the greatest transverse diameter of the cecum taken from a prone film in each of the 19 cases in which distention had developed after obstruction (Fig. 1a, b).

The range in size of the distended cecum in the control group extended from 3 to 10.5 centimeters (Fig. 1a). The distribution fell into a bell-shaped, normal curve. Three of the cases, artificially distended, reached a diameter greater than 9 centimeters. The size was below 9 centimeters in 97 cases. As a result, it was decided to use 9 centimeters as an emipiric cut-off point for comparison with cases in which distention had not been induced but had followed upon intrinsic distal obstruction.

The size of the cecum in the 19 cases of distention and obstruction ranged from 9.0 to 16.3 centimeters (Fig. 1b). This observation tended to bear out the significance of 9.0 centimeters as an arbitrary critical point. Any cecum of that size was to be considered in danger of perforation if an intrinsic large bowel obstruction was also present.

Confusion may develop if it is thought that perforation of the cecum simulates the explosive decompression of a tire blow-out.

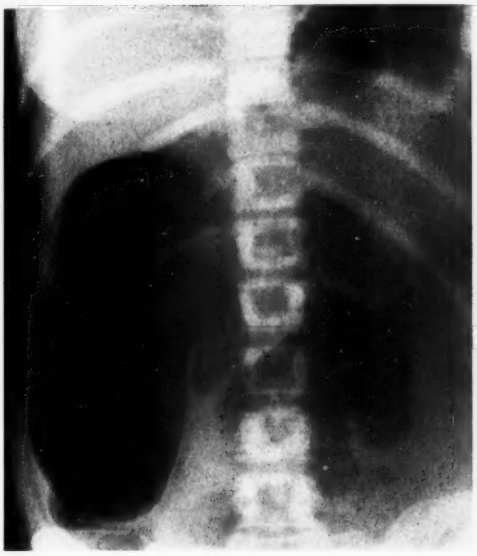

FIG. 4.

FIG. 5.

FIG. 4. O. H., female, aged 50 years, greatest transverse diameter of cecum was 11 centimeters. The loss of definition of the psoas margins and the generalized opacification of the abdomen were indicative of peritonitis. A companion radiolucent shadow following the margins of the distended cecum suggested the dissection of air along the cecal walls. Cecostomy on April 13, 1937 revealed perforation of the cecum with generalized peritonitis. Patient expired on April 15, 1937 and an adenocarcinoma of the rectosigmoid was found.

FIG. 5. E. C., female, aged 64 years, greatest transverse diameter of cecum measured 11.3 centimeters. There was evidence of massive distention of the cecum. The clearly defined psoas margins, the adequate definition of the bowel wall, and the absence of small bowel distention tended to exclude the consideration of generalized peritonitis and suggested the presence of impending perforation. Barium enema study, the same day, disclosed an intussuscepted lesion involving the left colon. Cecostomy on November 8, 1955 demonstrated the absence of peritonitis or perforation of the cecum. At further surgery on November 18, 1955 the adenocarcinoma which had intussuscepted was removed. The patient was subsequently discharged.

Usually the defense mechanisms of the body attempt to seal the perforation rapidly and effectively. This fact has been demonstrated in the cases from the literature and in the present series by consistent postmortem findings of adherent fibrin and mesentery about the rupture. It was reinforced by the measurements of the transverse diameter in the cases of perforation. The perforated cecum, in no instance, was reduced in size when compared with the over-all distribution of the group. In every case of perforation subsequently established at surgery or postmortem examination, the size of the cecum was beyond the critical measurement of 9.0 centimeters. There was no way to tell by size alone whether a particular cecum had already perforated through the mucosa.

It was concluded that the size of the cecum could be used to warn of impending perforation but that more classical roentgen signs had to be applied to decide whether complete perforation actually had occurred. Of these, the discernment of free air, while the most positive, was the most difficult of the established signs. Free air might simulate pneumatosis cystoides intestinalis with dissection along the walls of the ascending colon or so little air might be lost that it could remain in a small, loculated pocket obscured by other surrounding gas shadows. Greater reliance, therefore, was placed upon the definition of the psoas shadows, the properitoneal fat lines, and the distribution, contour, and shape of the bowel loops as indicators of peritoneal irritation. Absence of

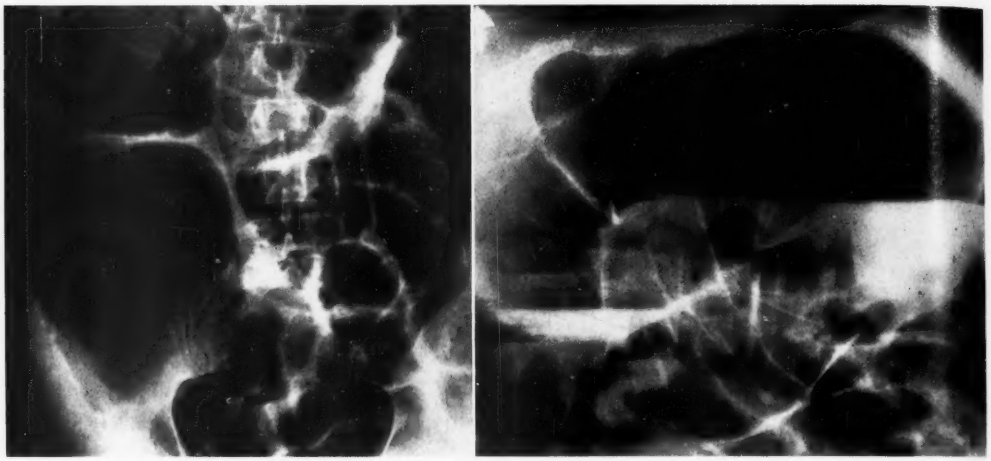

FIG. 6. E. O., male, aged 82 years, greatest transverse diameter of cecum was 12.5 centimeters. The recumbent and decubitus films revealed the cecal distention and loss of psoas margins and properitoneal fat lines. Together with a companion radiolucency around the lateral margin of the cecum suggesting the escape of air, these findings were thought to indicate perforation. Operation on December 6, 1955 revealed generalized peritonitis with perforation of the cecum along the anterior taenia walled off by adhesions. Cecostomy was done and an incarcerated femoral hernia which was not strangulated was revealed. The patient expired within 1 week.

visualized free air did not exclude the diagnosis of complete perforation (Figs. 2, 8).

CRITERIA FOR DIAGNOSIS

Using cecal size and the recognized roentgenographic findings in perforation, the following approach was adopted.

When it appeared that an obstruction of the colon had caused the cecum to distend, the largest transverse diameter of the cecum was measured on a prone film. A size of 9 centimeters automatically made the working diagnosis that of impending perforation. This diagnosis was maintained unless there was additional evidence of either loss of the psoas shadows, or disturbed bowel loops or free air at which time the diagnosis was changed to actual and complete perforation. Since distended small bowel loops could be present either with or without complete perforation this roentgen finding was not regarded as a pertinent sign. (Figs. 2 to 8).

The criteria, once established, were applied without a false result. Surgical intervention was carried out in each case of impending perforation. The precipitous fall in the immediate mortality rate which then devolved has been discussed. The uncommon occurrence of cecal distention as a complication of large bowel obstruction makes it difficult for a single group to collect a wholly statistically valid number of cases. But the importance, simplicity, verifiability, and apparent accuracy of the criteria presented recommend them to further use.

MECHANISM OF PERFORATION

Essentially 5 mechanisms have been proposed to account for the perforation of a normal cecum at a distance from the site of pathology. The influences of ischemia, bacterial toxins, and biochemical changes are uncertain. It is not known what critical pressure within the cecum will interfere with the blood supply and compromise the metabolic processes, and it is not yet possible to obtain indirect measurements of this pressure in the patient. The increased virulence of the normal bacterial flora observed in large bowel obstruction presumably hastens ulceration and necrosis. Grahame has reported that biochemical studies of 40 patients with large

FIG. 7.

FIG. 8.

FIG. 7. S. K., male, aged 79 years, greatest transverse diameter of cecum measured 13 centimeters. The large size of the cecum distended with fecal material, the absence of the psoas shadows, and the lack of definition of the properitoneal lines suggested complete perforation. The radiolucent lines overlying and following the cecal margins were consistent with free air due to perforation. Barium was introduced up to splenic flexure to exclude a left sided colon lesion. Operation on August 26, 1955 showed 3 large gangrenous perforations of cecum with free fluid throughout peritoneal cavity. At junction of cecum and ascending colon an annular adenocarcinoma was found. The patient died on September 18, 1955.

FIG. 8. F. T., male, aged 79 years, greatest transverse diameter of the cecum measured 14.2 centimeters. Cecal distention and the clearly defined psoas margins were considered to represent impending perforation. Cecostomy on October 3, 1947 revealed the absence of perforation or peritonitis. The anterior portion of the midsection of the cecum revealed a half-dollar area of extreme thinning with splitting of the anterior taenia. On November 4, 1947 a carcinoma of the transverse colon was removed.

bowel obstruction consistently revealed only a reduced plasma volume and a reduced serum albumin level.

The state of the ileocecal valve has been favored as the most important factor in deciding the events which follow an obstruction of the large bowel. The presence of an incompetent ileocecal valve has been held to protect against overdistention of the cecum by allowing the excess gas to regurgitate into the small bowel. Accordingly, perforation would occur only if the valve were competent. An incompetent valve would be associated with small bowel distention which, in turn, would be of diagnostic significance indicating that cecal perforation was unlikely. Clinical experience does not confirm the application of this principle, possibly because of the problems inherent in the recognition of an incompetent ileocecal valve.

Ravid has accepted the incidence of incompetent valves to be from 50 to 60 per cent, as demonstrated by barium reflux into small bowel during the administration of barium enemas. He believed that this explained why cecal perforation was a complication in only 2 out of 100 patients with a distal obstruction. But Fleishner, after reviewing reflux in as high as 90 per cent of a large series of enema studies, made the point that barium reflux was not to be equated with incompetence. The palpation and distention inherent to the enema examination were thought to introduce artefacts which prohibited any extrapolated inference with what might take place under other conditions.

The studies by Buirge on the anatomy and physiology of the ileocecal valve are not clinically applicable because of the confusing complexity of function in a valve which assumes a dual role of passiveness and activity in response to a variety of stimuli.

From a diagnostic standpoint, regarding the ileocecal valve as a potential safety valve would have been misleading in 3 cases, reported by Rack, in whom small bowel distention was displayed in the presence of perforation. It might be expected that cecostomy above all, performed before perforation, would mimic the action of an incompetent valve and rapidly reduce the size of a distended cecum. But it is not an uncommon experience to find that the degree of cecal distention remains unchanged for more than 5 days after cecostomy. There is 1 report of cecal perforation occurring soon after transverse colostomy had been completed as an attempt to relieve tension in the cecum.

In short, small bowel distention in the presence of a large bowel obstruction may be due to air swallowing, peritoneal irritation, or an incompetent ileocecal valve. A distinction as to cause may not be possible. But, an absence of small bowel distention may be assumed to be due to cecal valve competence and may serve to emphasize the distended size of the cecum. An appearance similar to a closed loop obstruction would then be found.

Finally, simple mechanical overdistention has been accepted as the other factor of prime importance in causing rupture. Clinically and experimentally, it has been found that in distention of the entire large bowel, the cecum is always the first portion to rupture. Two concepts have been used to explain this predilection of the cecum for perforation. First of all, hypertrophy of the bowel muscle has been found along the circular muscle coat located for an indeterminate length proximal to the site of an obstruction which has developed slowly. The likelihood of rupture within this segment is reduced in proportion to its hypertrophy. Secondly, an analogy from physics demonstrates that when 2 balloons, differing only in size, are blown up at the same rate of pressure, the larger balloon bursts first. This satisfactory explanation presumes that the tensile strength of the cecal wall is no greater than that of other segments of large bowel and that the cross section diameter of the cecum is larger than that of other segments.

In all likelihood it is the intermingling of the 5 mechanisms which determines the course of the cecum in an obstruction of the distal large bowel. The exclusive use of any one factor in explanation of the total picture has been injudicious.

SUMMARY

A method, based on roentgen measurement of the greatest transverse diameter of a distended cecum, had been suggested for the diagnosis of a state of impending cecal perforation in cases of large bowel obstruction. By encouraging surgery before cecal perforation, this concept appeared to be responsible for a striking reduction in the immediate mortality rate. Although this concept has been developed from a relatively small number of cases, it deserves further application because of its value in lowering the mortality rate from the 75 percentile levels reported consistently when surgery followed cecal perforation.

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DIRECT STIMULATION MYOGRAPHY AND ERGOMETRY OF HUMAN CALF MUSCLES WITH SUPPLEMENTARY OBSERVATIONS ON CALF ELASTICITY

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WE REPORT here the registration of calf muscle contractions in the human, the contractions being induced by rhythmic electrical stimulation. The method has been developed primarily to study muscle power and fatigability in peripheral arterial ischemia. Such a method is preferable to those ordinarily employed in that it depends but little upon the patient's volition. This article will describe the apparatus and the results in normal individuals, and in patients with arterial disease.

Hitzrot, Naide, and Landis thus studied intermittent claudication in 1936, using faradic stimulation. Schwab and de Lorme have similarly studied fatigue of the calf and other muscles stimulated with the oscillating current of the Batrow stimulator. We have utilized this same mode of stimulation, the limb being held in a specially constructed apparatus in which the foot acts against an adjustable load. The curves obtained of the individual tetanic contractions (myography), as well as the fatigue curve obtained by repeated rhythmic contractions (ergometry), allow a detailed analysis of muscle contraction.

Supplementary measurements have been made of the elasticity of the calf at rest ("basal elasticity") and will be mentioned. These data are of interest as giving some indication of pathologic change in the muscles; also, they are helpful in interpreting the characteristics of the contractions.

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APPARATUS

The apparatus consists of the stimulator and the ergograph.

The stimulator. According to information supplied by the manufacturer, the Batrow stimulator produces a highly damped oscillating current of high voltage, adjustable from 0 to 45,000 volts, and of low amperage, adjustable from 0 to 25 microamperes. The current is produced in pulses damped to make the first half cycle the predominant portion. The duration of the first half cycle is approximately 7 microseconds and, as we use it, the pulses are produced at a rate of 50 per second. The pulses reach the stimulating electrode in surges consisting of several pulses. Within each surge, the current intensity of the pulses builds up to a gradual peak, with a gradual fall to the current-free interval.

The output of the generator reaches the patient via a gas-filled glass electrode providing a condenser type of coupling to the calf. The electrode, laid on a wet cloth, covers an area of the calf of approximately 2½ by 5 inches and gives greatest stimulation when it is placed about halfway between the popliteal space and the thickest part of the calf. A larger return electrode consisting of a large hinged metal plate is placed on the opposite thigh. With the glass electrode placed as described, good contractions are obtained, apparently in all the leg flexors. Further work is necessary to establish how much of the stimulation is delivered directly to the muscle, and how much through the motor nerves.

In order to diminish the number of variables inherent in the stimulator, constant settings are maintained as follows: the polarity is set to positive, the pulse rate at maximum, and the surge rate 30 per minute. A faster rate does not allow time for adequate muscle relaxation between surges, while a slower rate invites volitional participation in the contraction. The one variable of the stimulation remaining is its intensity expressed in arbitary units. The stimulation produces some uncomfortable paresthesias in the limb which are minimized by gradually increasing the current intensity to a level at which good contractions are obtained.

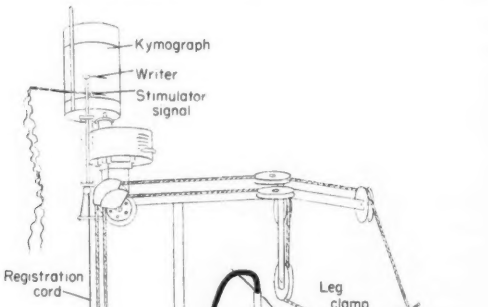

FIG. 1. Diagram of the ergometric apparatus. The arrows indicate the two directions of foot motion incident to calf muscle contraction.

The ergograph. A diagram of the ergograph is shown in Figure 1. It was designed to allow the patient to lie on his back, using his own shoe and stocking. The leg is supported on resilient foam rubber and is held in place by a rubber-lined clamp resting on the shin. The foot and ankle extend beyond the table in a predetermined position, with the shoe resting on a metal plate. Calf muscle contraction produces motion of the foot which is unhampered in its direction, plantar flexion being accompanied by posterior displacement of the entire foot. The foot moves against the load of a hanging variable weight. The weight is connected to the foot plate by means of a rope passing over pulleys and attached to the plate in such a way that both vectors of the foot motion are summated when the calf muscles contract.

Registration of movement is accomplished by a cord passing from the weight to a stylus, which writes on a kymograph. An electromagnetic signal, connected with the output of the stimulator, shows the time of each surge of stimulation. It should be recalled, however, that effective stimulation may be limited to the central part of each surge when the pulses are of maximal intensity.

ANALYSIS OF RESULTS

The normal myogram and ergogram. A normal myogram is shown in Figure 2. The ascending limb represents calf muscle contraction, and the descending limb indicates relaxation. The contraction is brisk, rising to an acuminate peak and falling precipitously when stimulation ceases. We cannot explain the finer structure in the contraction peak. Theoretic possibilities include: lack of fusion of electrical pulses within the surge, varying rates of arrival of stimulation via nerves or muscle to the muscle bundles contracting, different rates of response of the fast-acting pale fibers of the gastrocnemius muscle and the slower red fibers of the soleus, and finally slight contraction of the extensors induced by their being suddenly stretched.

The relaxation phase is marked by a sharp dip which we have designated the "relaxation notch," followed by a rise and smaller notch, the "precontraction notch," occurring prior to the beginning of stimulation. Inasmuch as the presence of these notches is characteristic of the response of normal nonfatigued muscle, an explanation of their formation is in order. Because the relaxation notch occurs early in the relaxation phase, the possibility was suggested that it might be due to passive extension of the foot caused by the momentum of the falling load. This theory was substantiated by: (1) the increase in depth of the notch when the load was increased; (2) its diminution and disappearance when fatigue caused tonus to increase, thus lessening the ability of calf muscles to stretch (Figs. 3 and 4); and (3) a positive correlation between the "basal elasticity" (*vide infra*) of the calf and the depth of the notch. The presence and depth of the precontraction notch are correlated with the relaxation notch.

The following appears to be the most plausible explanation of the precontraction notch. The sudden and sharp stretching of the calf muscles caused by the falling weight at the time of the relaxation notch evokes a sudden contraction of the calf muscles which results in the rise of the weight and the curve. This in turn produces a sudden stretch of the extensor muscles of the leg, which likewise react by contraction, causing foot extension with fall of the weight and the curve in the precontraction notch. The relaxation of the extensors is followed in me-

diately by electrical stimulation and a new calf muscle contraction phase.

There is little doubt that these notches could be obviated if a strain gauge system, such as Ferguson used in animal work, were substituted for the hanging weight. We have hesitated to make such a change, however, because the present method allows one to detect more readily movement of the patient or his volitional participation, and what is more important, we find the two notches give considerable information as to basal elasticity or increased tonus of the calf muscles.

In addition to the shape of the myogram, the height of contraction, with reference to weight lifted, and the intensity of stimulation required are important attributes of the muscle, and presumably of its nerve and blood supply.

Muscle power, and susceptibility to fatigue are particularly well brought out in the ergogram, made by continuing stimulation until a plateau is reached or the subject complains of discomfort. It is to be noted that, except for the registration of a few early contractions as shown in Figure 7, the ergograms presented were made with the kymograph running slowly, with consequent lack of detail of each myogram. Subjects experience least discomfort if the stimulus intensity is started close to zero and increased gradually. Usually, we do not start registration until the intensity has reached the level at which it is thereafter maintained. The records, therefore, usually fail to show the treppe phenomenon, which is concomitant with the early unrecorded contractions.

The normal ergogram (Fig. 3) shows a fairly constant response for 15 to 20 contractions. Shortly thereafter the amplitude of contraction falls, while the base line rises, indicating an increased tonus. If the load is only moderate for the individual, a secondary rise in amplitude and a fall in tone, characteristic of "second wind" is seen in a minute or two, slowly subsiding again to a plateau of effect which is then maintained for many minutes. With an excessive load, the changes of fatigue are progressive until

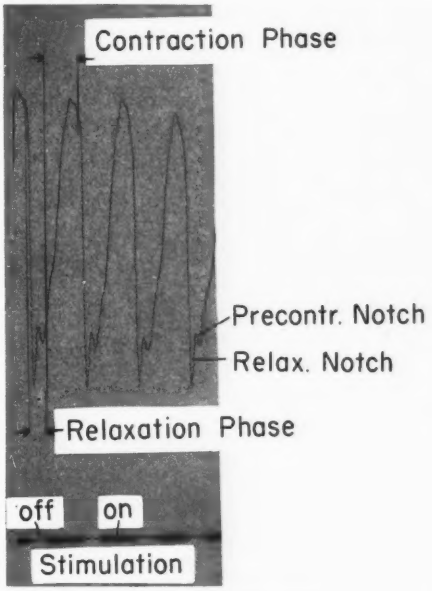

FIG. 2. Phases of the normal myogram.

there is little or no noticeable contraction. The limb may then be said to be in a state of contracture.

The changes of fatigue occur rapidly and in an exaggerated degree if one produces ischemia by compression of the femoral artery during the test (Figs. 3 and 4). In Figure 4, the speed of the kymograph was increased at intervals during such an experiment to obtain individual myograms at various stages of fatigue and its recovery. The rapid increase in tone causes a disappearance of the relaxation and precontraction notches. This flattening of the interval phase is accompanied by a similar flattening of the contraction peak, the two limbs of the myogram showing more gradual slopes. These features are progressively exaggerated as amplitude falls, and finally reaches zero, just before release of the artery. In recovery, the normal features of the contraction gradually return, but tone never falls to its primary level unless the limb is allowed to rest for several minutes. Most often, in normal limbs, this sequence gives rise to a better performance in a second test.

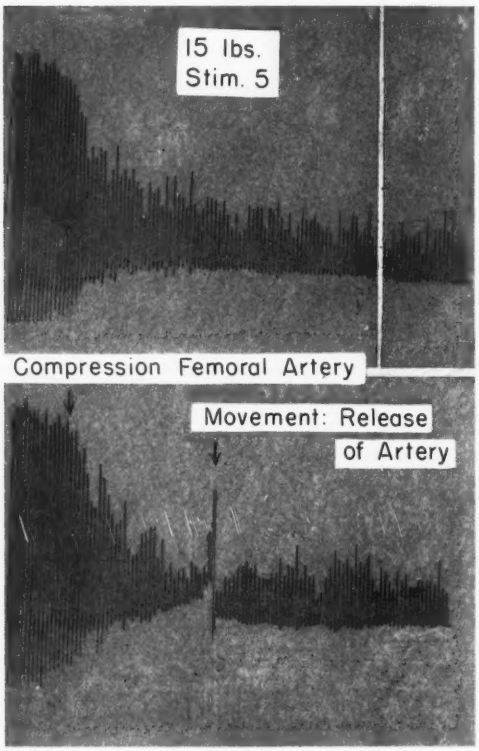

FIG. 3.

FIG. 3. Above, Normal ergogram; total time, 4 minutes; energy value (for 3 minutes), 22. Below, Changes induced by arterial compression; total time, 3½ minutes; energy value (for 3 minutes), 22.5.

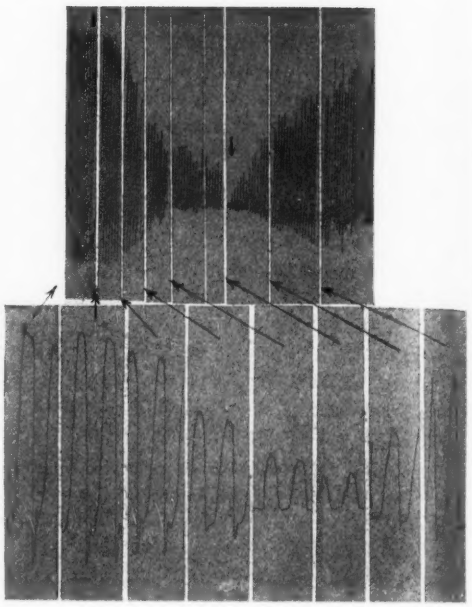

FIG. 4.

FIG. 4. Above, Normal ergogram in another subject with femoral artery compressed between upper arrows. Below, Myograms made by increasing speed of kymograph at indicated points during the experiment. The total time was 4 minutes; energy value (for 3 minutes), 41.2.

While the height of contraction is an indication of muscle power, it should be remembered that, within limits, an increased loading of the muscles produces a greater stretch and a correspondingly increased excursion during contraction. Fatigue comes on more quickly, however. The production of fatigue is not painful to most normal subjects unless it is accompanied by ischemia, in which case there is present severe cramping pain, as lack of appreciable contraction is approached.

The ergometric records show impressive evidence of the well known sensitivity of muscle to the well-being of the individual, muscle conditioning, and general fatigue—facts noted by Mosso and other physiologists of the last century. We believe these variations are evidence of the reliability of the method, since the direction of the variations has been consistent with other signs of the condition of the subject.

Mensuration of the ergometric curve. The assignment of a numerical value to the ergometric curve facilitates comparison of muscle performance between individuals and between repeated examinations of the same individual. It can be shown that the energy expended in producing the ergometric curve is equivalent to the total area of that curve. We have thus chosen to use the area of a 3 minute ergogram, expressed in square centimeters, as an "energy value." The rate of stimulus has been the same for all tests and the contractions have been recorded at the same slow speed of the kymograph. The measurement of the area has been done by the use of a planimeter.

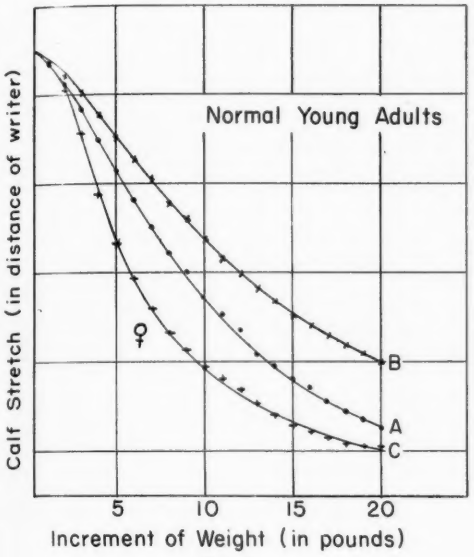

FIG. 5.

FIG. 5. Normal curves of calf elasticity. *A* is an average reading. *B* and *C* indicate usual normal range. Elasticity values: *A*, 10.8; *B*, 8.9; *C*, 11.3.

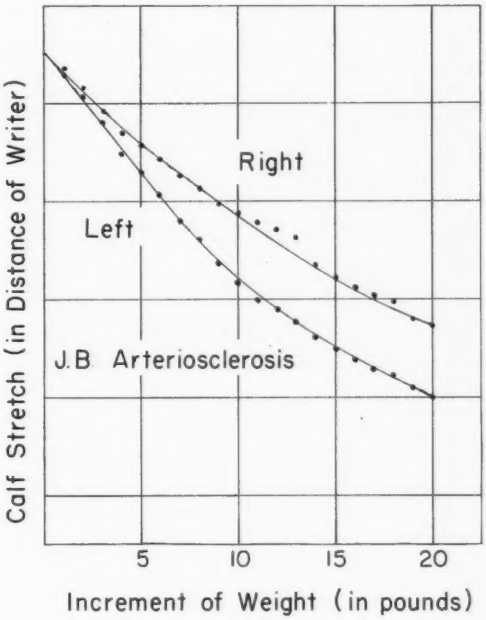

FIG. 6.

FIG. 6. Calf stretch curves of a patient with arteriosclerosis and severe ischemia. Both legs show a lessened elasticity; the value for the left leg is 8.9; for the right leg 7.1. The energy value for the left leg was 11.0; for the right leg, 3.8.

We found that an ergometric curve of 3 minutes' duration provides a good sampling of the subject's performance. In such a curve, there is usually a balancing of the effects of the size of the load and duration of the experiment so that the energy value for a given limb is almost the same whether a medium or a heavy load has been used. Our objection to converting the value to actual units of power is that we have no way of determining the efficiency of our method of stimulation with regard to the proportion of calf muscle fibers stimulated, and the adequacy of stimulation. A minor objection is the difficulty involved in the exact measurement of friction and other mechanical factors in the device.

At the most frequently employed stimulation intensity of 5, 6 normal subjects working against loads of 10 to 20 pounds achieved energy values varying from 15.5 to 42.5. An increase in stimulation intensity increased the energy value moderately, while a change in weight in this range had but little effect.

MEASUREMENT OF BASAL CALF ELASTICITY

Measurement of basal elasticity of the calf was made by placing the limb in the ergograph, with the stimulation omitted. Passive extension of the foot was recorded on the kymograph paper as 1 pound weights were added to the load to a total of 20 pounds. We have determined that approximately 3/4 pound of force acts against the foot prior to the addition of any weights, this being comprised of the pull of the foot plate, the weight of the load carrier, and the tension of a spring in the writing mechanism.

Figure 5 shows 3 curves of normal subjects obtained in this way, and the extremes to be expected. In all instances the curve is exponential, the length of stretch falling off markedly as more weight is added. Stretch

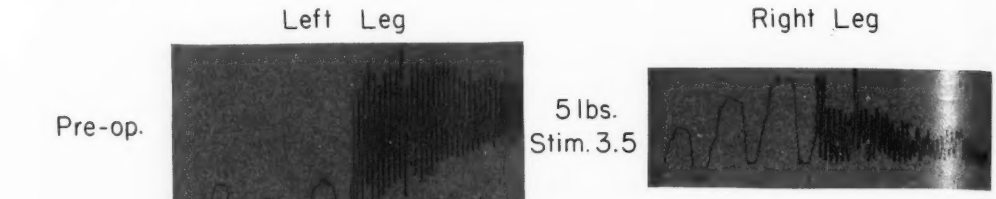

FIG. 7. Application of the method to a patient with arteriosclerotic occlusion of the aortic bifurcation. The preoperative readings show the abnormal individual contractions and ergometric curves characteristic of ischemia. (Energy values: left, 11.2; right, 4.1.) Operation (endarterectomy) restored excellent peripheral pulses, but the response at 2½ months was further diminished. (Energy values: left, 2.8; right, 2.4.) At 6 months the response shows a fair approximation to normal. (Energy values: left, 23.3; right, 15.9.)

over the whole range is less in the case of the heavily muscled individual (*B*), while it is greater than average in a slender girl (*C*). An exact relationship could not be established between the amount of stretch and circumference of the calf, variations of muscle shape and muscle conditioning undoubtedly influencing the result. It is reasonable to assume that the curves are influenced mainly by elasticity of the calf muscles, if one excludes abnormalities of the fasciae and of the structures of the ankle joint. The shape of the curves is in accord with those known to be standard for isolated muscle in the experimental animal, and with those found by Ralston and his associates for live human muscle examined in tendinoplastic amputation stumps. We shall use the expression basal elasticity to distinguish this type of measurement from the diminishing state of elasticity incident to the increased tonus of fatigue.

As with the ergometric curves, the assignment of a numerical value to the elasticity curve is useful for ready comparison. In this instance we have labelled the height of the curve in centimeters as the "elasticity value." The elasticity values for our normal subjects were found to range from 8.7 for a heavily muscled male leg to 12.1 for the limb of a slender young woman.

A diminished basal elasticity is indicated by an upward shift in the elasticity curve; it may also be inferred by a lack of the notches in the relaxation phase of the myogram during the first few contractions examined. Our results confirm the expectation that a lessened stretch of the calf is associated with a lessened height of contraction (Fig. 6).

RESULTS IN ISCHEMIC LIMBS

The response of the ischemic limb is characterized by a sluggish contraction of low power and low amplitude, with a sluggish

and incomplete relaxation. The myographic curves obtained at the outset in such a limb resemble those from fatigued normal limbs. Power is greatly diminished, and it is not at all unusual to find that a load of 10 pounds allows no excursion of the foot. The ergometric tracings show a strikingly rapid increase in tonus with a rapid loss of amplitude (Fig. 7). It should be noted that other disorders may give similar results. Thus, we have seen similar curves in very weak patients and in the presence of neuritis.

While few patients complain of leg "pain" or "cramp," the complaint is somewhat commoner than among normal subjects. In some patients even the limited response requires an unusual intensity of stimulation. Further study is required to determine if this fact is due to nerve or muscle damage.

Determining the energy value of these patients is often hampered by the necessity of stopping the test before 3 minutes have elapsed because of discomfort or cessation of contractions. In these instances, we have extrapolated the tracing to the 3 minute mark prior to planimetry. While a gradation of energy approaching that of normal subjects may be expected, depending upon varying degrees of ischemia, our untreated patients have most commonly shown values of 3 to 12, with unusual readings below or above range. When the value is less than 1, it is difficult to determine accurately, and we have labelled the value as "negligible."

Basal elasticity is lessened in most limbs in which severe ischemia has been present, suggesting muscle damage and fibrosis although disuse may also diminish elasticity (Fig. 6). Elasticity values in ischemic limbs have usually ranged from 7 to 11. Ergometric performance is generally poorer in limbs with low elasticity values than in limbs with higher values. That this correlation is not invariable, undoubtedly simply means that muscle elasticity is but one factor influencing the contraction.

Improvement of the blood supply of the muscle is accompanied by corresponding increase in both elasticity and energy values.

SUMMARY

The calf muscles of normal subjects and of arteriosclerotic and other patients with muscle ischemia were stimulated by the rhythmic oscillating current of the Batrow stimulator, with the foot acting against a variable load. The myograms of the individual tetanic contractions, as well as the ergograms of repeated contractions, allow an estimation of the rapidity, power, and amplitude of contraction, and the extent of relaxation. Changes in muscle tone are readily apparent. This method of study of intermittent claudication has the advantage that it does not depend upon the patient's volition.

Data on the elasticity of the calf tissues were obtained by omitting stimulation, and noting the degree of extension of the foot after adding graded weights to the load.

The energy expended in producing the ergometric curve is equivalent to the total area of that curve. For purposes of ready comparison, the area of a 3 minute ergometric curve, expressed in square centimeters, was utilized as an "energy value." A similar term, the "elasticity value," was used for the curves of calf elasticity, consisting of the total excursion of the writing pen expressed in centimeters.

The ischemic limb differs from the normal by responding with a sluggish contraction of low power and of low amplitude, and with a sluggish and incomplete relaxation. The latter is related to a diminution in elasticity at rest, as well as to the rapid development of a high tone, characteristic also of fatigued normal muscle. These qualities are emphasized in the ergometric curve made by stimulations of several minutes.

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HISTOLOGIC TECHNIQUES FOR THE DIFFERENTIAL STAINING OF BURNED AND NORMAL TISSUES

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MUCH EXPERIMENTAL WORK on burns has been hampered by the inability of an investigator to determine precisely the depth of injury produced. Comparisons of the effects of various exposure times and irradiances, comparisons of the ability of different agents to protect against thermal energy, and predictions of heat flow through tissue and thermal damage to tissue are dependent on the demonstration of the level at which destruction ceases and normal structures remain. The common histologic techniques for staining experimentally burned skin necessitate a highly subjective interpretation of the depth of injury. The investigator must be experienced in histology and able to distinguish between minute differences in cell composition and shape, and two such experts do not always agree on the result obtained.

It would be very useful to be able to determine rapidly and accurately the depth of injury produced by an experimental burn, and for this reason a search was made for staining techniques which would yield a striking color contrast between normal and burned tissues. It was borne in mind that these methods, to be most useful, should be relatively simple and reproducible in any tissue laboratory, and that workers with little training in micropathology should be able to interpret the results without difficulty. Such techniques have been found and their reliability and accuracy have been demonstrated in well over 1,000 experimental burns.

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EXPERIMENTAL METHODS

The experimental animals were young Chester White pigs anesthetized with intraperitoneal dial in urea-urethane in doses of 70 milligrams per kilogram of body weight. The hair was removed with electric clippers and the skin was gently washed. A heat source consisting of a modified 24 inch Army carbon arc searchlight (3, 6) produced burns which varied from mild erythema to severe, full thickness damage. The port which controlled the size of the burn was 1.7 centimeter in diameter. Exposure times of from 0.3 to 30.0 seconds and irradiances of from 32 calories to 0.16 calorie per square centimeter per second were used.

Eighteen to 24 hours after the burns were placed, biopsies were taken across the injured areas so that normal tissue was included on each side of the burn. The biopsies were fixed in 10 per cent formalin or Bouin's solution and embedded in paraffin.

Various staining solutions were selected for trial because results from their use in standard histologic techniques led us to believe that they might aid in the differential staining of burned skin. When a technique offered promising results, staining and differentiating times were altered to achieve ideal staining conditions. Sections were then examined by both experienced and inexperienced microscopists to determine what color combinations could be interpreted most easily and most accurately. The final step consisted of altering staining, differentiating, washing, and counterstaining times so that the desired end result could be reached with large groups of slides and without individual attention to each slide.

The methods which have proved to be accurate and extremely useful in determining the depth of experimental burns are given in the outline which follows. They are modifications of standard techniques and employ stains common in every histology laboratory.

OUTLINE OF STAINING METHODS[1]

Method I. A modification of Verhoeff's stain

1. Fixation: 10 per cent formalin.
2. Embedded in: paraffin.
3. Preparation of staining solution: With the aid of heat, dissolve 1 gram of hematoxylin (chemically certified) in 20 milliliters of absolute alcohol. Filter and add 8 milliliters of a 10 per cent aqueous solution of ferric chloride and 8 milliliters of an iodine solution made by dissolving 2 grams of iodine and 4 grams of potassium iodide in 100 milliliters of distilled water.
4. Staining schedule:
   a. Remove paraffin from sections in the usual manner.
   b. Immerse sections in the above staining solution for 20 to 30 minutes.
   c. Differentiate in a 2 per cent aqueous solution of ferric chloride. A rack containing about 25 slides can be dipped up and down in this solution 20 times or so in 20 to 30 seconds.
   d. Wash immediately and thoroughly in fresh tap water.
   e. Place in 95 per cent alcohol for 1 minute.
   f. Wash in running tap water thoroughly for 5 minutes.
   g. Counterstain for 15 seconds in van Gieson's stain.
   h. Dip slides once in tap water.
   i. Dehydrate in 95 per cent alcohol followed by absolute alcohol.
   j. Clear in xylene.
   k. Mount.

Results:

Normal epidermis: gray.
Burned epidermis: pale yellow.
Normal dermal collagen: yellow-brown.
Burned dermal collagen: black or purple depending on the concentration of tissue.

Precautions:

1. The staining solution should be used within 24 hours.
2. Fresh staining solution should be used after each 75 slides.
3. Differentiation in 2 per cent aqueous ferric chloride is accomplished more rapidly than in the standard Verhoeff stain. Until an exact time is established, a single slide may be examined in water to determine the degree of differentiation. Depending on the result, the slides may be either restained or may be differentiated further.
4. Particularly when staining a group of slides at one time, the last washing in tap water must be thorough.
5. A short counterstaining time yields slides which may be interpreted very rapidly. The more brilliant colors produced by a longer counterstaining time are less easy to read.

Method II. Buffered azure eosinate method (From Lillie's modification of Nocht's method. The *p*H level recommended by us is 3.95.)

1. Fixation: 10 per cent formalin.
2. Embedded in: paraffin.
3. Buffered solutions. Prepared with M/5 sodium phosphate and M/10 citric acid to give a *p*H level of 3.95. The method is found in standard histologic technique texts.
4. Staining solution: To 3.5 milliliters each of 0.1 per cent aqueous azure A (chemically certified) and 0.1 per cent eosin B (chemically certified), add:
   a. 2 milliliters of the buffer mixture.
   b. 5 milliliters of acetone (chemically pure).
   c. 26 milliliters of distilled water.
5. Staining schedule:
   a. Remove paraffin from sections in the usual manner.
   b. Stain 1 hour in the staining solution.
   c. Dehydrate in 2 or 3 changes of acetone.
   d. Clear in 1 change of acetone and xylene and 2 changes of xylene.
   e. Mount.

Results:

1. Normal epithelium: blue.
2. Burned epithelium: pink.

Method III. From Fraenkel's orcein method

1. Fixation: 10 per cent formalin.
2. Embedded in: paraffin.
3. Staining solutions:
   Solution A. A stock solution is prepared by mixing the following: orcein (chemically certified), 1.5 grams; 95 per cent alcohol, 120 milliliters; distilled water, 60 milliliters; nitric acid, 6 milliliters. A sufficient amount of this solution is added to 3 per cent alcoholic HCl to give a dark purple-brown color.
   Solution B. Dissolve 0.25 per cent indigo carmine (chemically certified) in saturated aqueous picric acid.
4. Staining schedule:
   a. Remove paraffin from sections in the usual manner.

[1] The procedures presented here are modified from techniques described in 1946 by Conn and Darrow (2).

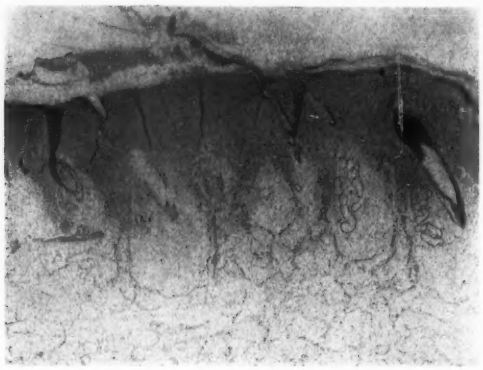

FIG. 1. Burned porcine skin stained with hematoxylin and eosin. Normal dermis on the right, burned dermis on the left. ×9.

b. Stain for 5 minutes with Orth's lithium carmine.
c. Differentiate rapidly in 1 per cent alcoholic hydrochloric acid.
d. Stain 24 hours in solution A.
e. Differentiate lightly in 80 per cent alcohol.
f. Stain 1 minute in solution B.
g. Rinse in 3.5 per cent acetic acid.
h. Dehydrate quickly in 95 per cent and 100 per cent alcohol.
i. Clear in xylene.
j. Mount.

Results:

1. Normal collagen: green.
2. Burned collagen: orange-brown.

Precautions:

1. Orth's lithium carmine is used in Fraenkel's orcein method to stain the nuclei. Burned tissue will retain some of this color, and one should not attempt to destain this by thorough differentiation.
2. After the long staining period in solution A, burned tissue will have a dirty red color. Differentiation in 80 per cent alcohol should not remove this color.
3. A short staining period in solution B is quite satisfactory and the longer periods have no advantage. Even the 1 minute allowed can be decreased if desired.

RESULTS

Method I. A modification of Verhoeff's stain. This staining technique, which consists of slight modifications in the Verhoeff elastic tissue stain, is probably the most useful one for ordinary work. If it is carried out in the manner prescribed there will be a marked color difference between burned and normal tissue (Figs. 2 and 3), and the results are so consistent that duplicate staining is not necessary. Normal epidermis is gray, burned epidermis is yellow. Normal dermal collagen is yellow, burned collagen is black or purple.

Method II. A buffered azure-eosinate method. This technique is chiefly used in differentiating burned and normal epithelium. For determining the depth of dermal injury it is even less useful than an ordinary hematoxylin and eosin stain. With the azure-eosinate method, epithelium damaged by heat is pale pink while normal epithelium is

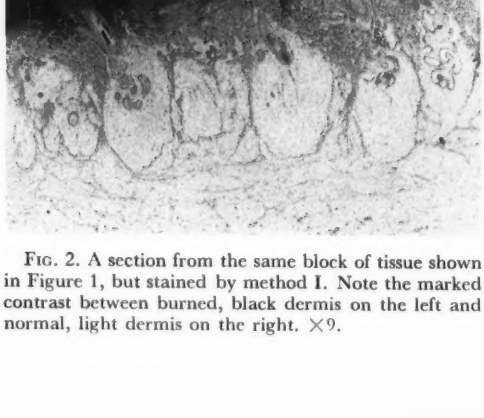

FIG. 2. A section from the same block of tissue shown in Figure 1, but stained by method I. Note the marked contrast between burned, black dermis on the left and normal, light dermis on the right. ×9.

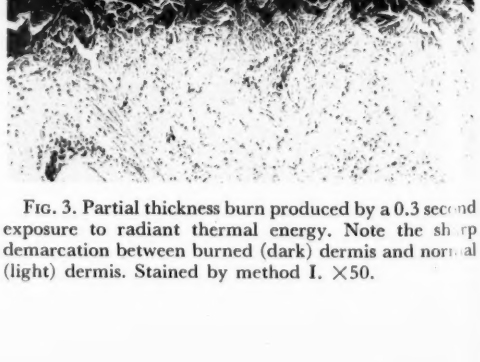

FIG. 3. Partial thickness burn produced by a 0.3 second exposure to radiant thermal energy. Note the sharp demarcation between burned (dark) dermis and normal (light) dermis. Stained by method I. ×50.

FIG. 4. Mild, transepidermal burn stained by method II. Normal epidermis on the left, damaged epidermis on the right. ×60.

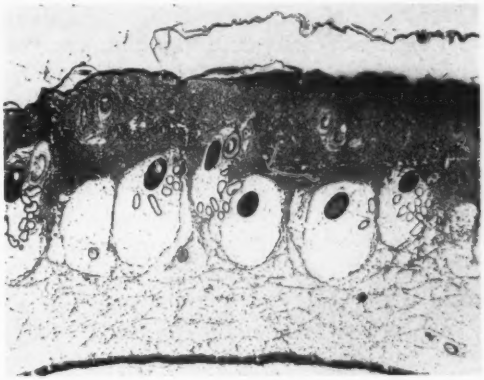

FIG. 5. Partial thickness burn stained by method III. Normal skin on the left and burned skin on the right. ×6.

blue. Even when injury is confined to the superficial layers of the epidermis the color contrast is prominent (Fig. 4).

Method III. An orcein connective tissue stain. This is less useful than method I because the color contrast between normal and burned epidermis is not so marked and nuclear staining requires some care. However, the difference between normal, green collagen and orange-brown collagen which has been burned cannot be mistaken (Fig. 5). It has, therefore, been useful in confirming the reliability of method I.

DISCUSSION

In many experiments with burns it is necessary to determine as accurately as possible the depth of injury resulting from a particular thermal insult. In this laboratory, specimens of more than 3,000 burns have been stained with hematoxylin and eosin. With this technique, if staining conditions are well controlled, there is a color difference between acidophilic, burned epidermis and basophilic, normal epidermis (Fig. 6). However, when many slides are stained simultaneously, even this difference is not consistent. Overstaining with hematoxylin will provide some color contrast between normal and burned dermal collagen, but it is prominent only in the more superficial, severely injured areas and is not reliable for determining the complete extent of an injury. Also, such overstaining does away with the contrast between normal and burned epidermis. Mallory's stain and Masson's trichrome stain are of equally limited value. With all three techniques one must determine the extent of injury by the size and shape of nuclei and by almost insignificant differences in the composition and color of collagen (Figs. 1 and 6). This procedure is very time-consuming, and it is disconcerting how often experienced microscopists disagree on the findings.

Because the methods presented here provide such a marked color difference be-

FIG. 6. Partial thickness burn stained with hematoxylin and eosin. Normal skin on left, burned on right. Damaged epithelium easily identified, but not collagen. ×60.

tween normal and burned tissue the slides can be read easily and rapidly. The accuracy of the methods has been checked by staining sections from the same blocks of tissue by a number of techniques. Long, careful examination of the hematoxylin and eosin sections and a much faster examination of the specially stained sections lead to the same estimate of the depth of damage.

Method I, which seems to us to be the most useful one for routine work, has already proved invaluable in experimental work on the effects of superimposing two radiant energy thermal burns (4), on the use of flash creams in protecting bare skin against radiant thermal energy (1), and on the prediction of the depth of injury by surface appearance of burns (5).

SUMMARY

1. A search was made for histologic techniques which would provide a striking color contrast between normal and burned tissue.

2. The most useful techniques for the differential staining of burned and normal tissues are described and illustrated.

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REPLACEMENT OF A TRICUSPID VALVE CUSP BY A HOMOLOGOUS CUSP IN DOGS

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RHEUMATIC DISEASE of the mitral valve of the stenotic type is usually amenable to surgical treatment, but there is a class of patients, disabled to greater or lesser degree, in whom surgical correction of mitral stenosis has nothing to offer in treatment. Their disability results from regurgitation through an incompetent mitral valve more than from obstruction by a stenotic valve.

There have been many ingenious operations devised to correct mitral incompetence but all leave much to be desired. Many of the experimental series have been concerned with tricuspid insufficiency, which is easy to produce by resection of a cusp and on which an open operation can be performed without the danger of systemic air embolism.

Autogenous cusp replacement. Inverted vein or pericardial grafts have been sutured in a cusp form to replace experimentally damaged cusps. Murray, Wilkinson, and McKenzie used autogenous vein and Templeton and Gibbon used both vein and pericardium. In the latter series 8 dogs survived more than 3 weeks. The 4 dogs which had not yet been sacrificed at the time of their report all had systolic murmurs, and of the 4 dogs sacrificed 2 had useless inelastic cords replacing the grafted cusp, while in the other 2 the graft was not apparently functioning.

Autogenous endothelium-lined slings or hammocks. In theory a broad flexible sling could be placed across the atrioventricular valve orifice on the ventricular side, which would block the orifice during ventricular systole and flap back to allow filling during diastole. Bailey, O'Neill, Glover, Jamison, and Redondo-Ramirez (2) and Logan and Turner have used parietal pericardium in this way. The results, however, are unsatisfactory. This fact was shown by Moore and Shumacker who found fibrosis and degeneration in slings of inverted artery, inverted vein, tendon, pericardium, and rectus sheath with peritoneum. As Wilson discovered in 1930, "from (two weeks) until about four months after transplantation the strip gradually acquired a smooth, rounded and usually perfectly regular outline, and a tough inelastic consistence. No change occurred subsequently."

Use of other autogenous tissue to block the valve orifice. O'Neill and Glover (3) have inverted the left auricular appendage through the mitral orifice in the hope of providing a baffle against which the aortic cusp could close. Hayward used this method in 2 women without more than temporary success. Bailey, Jamison, Bakst, Bolton, and others (1) have used a pericardial strip to suture together the mitral cusps posteriorly.

Plastic prostheses. The name of Harken and his coworkers is attached to various modifications of a lucite ball used as a baffle to occlude the mitral orifice during ventricular systole. They state that the results are encouraging.

Methods of reducing the circumference of the valve orifice. Davila, Mattson, O'Neill, and Glover have placed a ligature around the atrioventricular ring to reduce the circumference of the ring and so reduce valvular insufficiency.

The present study was undertaken to test the possibility of transplanting a normal valve cusp from a donor animal to replace one damaged by disease. The tricuspid

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TABLE I

Dog No.	Interval before sacrifice, weeks	General condition at time of sacrifice	Condition of tricuspid homograft at time of sacrifice: Healed to annulus and ventricle	Competence	Thickening of cusps and chordae	Calcification	Cartilaginous metaplasia
1	27	Good	Complete	Moderate	+	+	+
2	30	Good	Complete	None	+++	++	+
3	29	Good	Complete	None	+++	−	+
4	29	Good	Complete	None	+++	++	+
5	26	Good	Partial separation at annulus	None	+++	++	+
6	5	Distemper	Complete	Moderate	Slight	No histology	No histology
7	26	Good	Partial separation at annulus	None	+++	++	+
8	4	Distemper	Complete	Good	Slight	No histology	No histology
9	26	Good	Total separation of papillary muscle from ventricular wall	None	++++	+	+
10	26	Good	Complete	Moderate	+	+	+

valve in dogs was used in order to overcome the problem of air embolism which is found in performing open operations on the left side of the heart.

METHODS

Procurement of the homologous cusp. Immediately before operation a healthy adult dog was heparinized and sacrificed under nembutal anesthesia by arterial exsanguination. The blood was collected in glass bottles and was used for transfusion during valve replacement. The heart was removed aseptically, the right ventricle laid open, and the anterosuperior cusp of the tricuspid valve carefully dissected out, together with a fringe of the fibrous annulus, the chordae tendineae, and the papillary muscle. It was placed in physiologic saline solution until it was inserted about 30 minutes later.

Production of tricuspid insufficiency and insertion of the homologous cusp. Healthy adult mongrel dogs were premedicated with morphine and atropine and anesthetized with ether on a mask. Anesthesia was continued with an air-ether mixture administered by intermittent positive pressure through an endotracheal tube. Under aseptic conditions the right or left common carotid artery was exposed in the neck, and thoracotomy was performed through the fifth right interspace. The azygos vein was ligated and tapes were passed round superior and inferior venae cavae to provide cardiac inflow occlusion. A third tape was placed round the descending part of the arch of the aorta to exclude the lower part of the body from the intra-arterial transfusion. The pericardium was opened and stay sutures placed in the lateral wall of the right atrium. A curved Pott's clamp was applied to the lateral wall of the right atrium and the atrial wall was incised. The heparinized arterial blood was now run into the common carotid artery in a central direction at a rate of approximately 50 cubic centimeters per minute (about 5 c.c. per kilogram per minute). Cardiac inflow occulsion was produced and the aortic tape tightened. The Pott's clamp was then removed and the anterosuperior cusp of the tricuspid valve was excised under direct vision. A clamp was placed on the papillary muscle to guide the insertion of the homograft.

The homograft cusp was introduced. Its papillary muscle was transfixed by a silk suture both ends of which were passed through the right ventricular wall. When this was tied at the end of the operation it approximated the homograft papillary muscle to the stump of the recipient papillary muscle. A continuous silk suture now united the fibrous base of the grafted cusp to the fibrous annulus at the site of excision of the cusp. Each end of the grafted cusp was carefully approximated to the next cusp

The right side of the heart was allowed to fill with blood, the Pott's clamp was reapplied, and all tapes were removed. The time of cardiac occlusion was usually 8 to 10 minutes. The transfusion was stopped and the carotid artery ligated. The two ends of

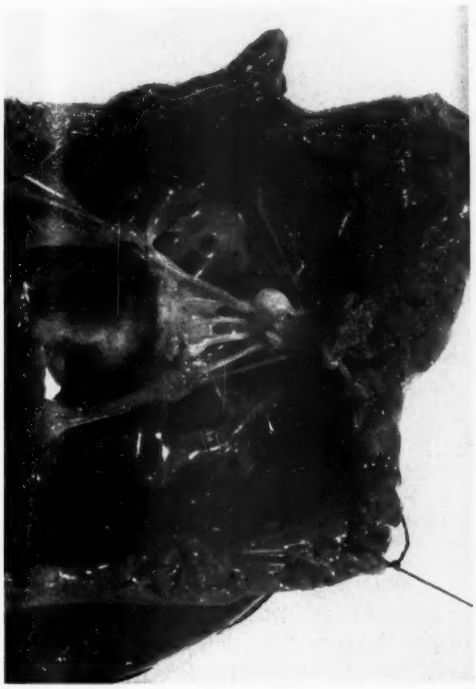

FIG. 1. Dog 1, 27 weeks after tricuspid homograft. The right ventricle has been opened. The grafted cusp is thickened and opaque.

FIG. 2. Dog 10, 26 weeks after tricuspid homograft. The right ventricle has been opened. The grafted cusp is thickened and opaque.

the papillary muscle suture were tied, after taking a bite of myocardium with each, over a free muscle graft from the chest wall. The atrial incision was closed, and the chest was closed after inflation of the lungs.

When the amount of blood infused was much in excess of blood loss, venesection was performed.

RESULTS

Ten dogs survived longer than 2 weeks and were suitable for assessment of valve structure and function (Table I). Two dogs died of distemper and the remaining 8 were sacrificed after 6 to 7 months. In all the heart was removed, tricuspid valve competence was tested by infusion of water into the right ventricle while the valve was observed and the gross and microscopic appearances of the valve were recorded. In the 2 dogs which died after a month of distemper the valve was found to be moderately, though not completely, competent, but in only 2 of the longer survivors was there found to be any competence in the valve at all. In all except 1 the insufficiency was produced by thickening of the grafted cusp and of its chordae tendineae and by loss of its normal resilience. In the 1 exception, the papillary muscle had pulled away from the ventricular wall altogether and the graft was represented merely by a knob of calcified hyaline connective tissue showing cartilaginous metaplasia.

The 2 best results (dogs 1 and 10) are illustrated in Figures 1 and 2. The opacity and thickening of the grafted cusp are obvious in each case.

Microscopically the outstanding changes were the thickening of the cusp due to laying down of hyaline fibrous tissue (Fig. 3). In some cases throughout the cusp, and

FIG. 3. Dog 3, hyalinization and commencing cartilaginous metaplasia near the annular attachment of a homografted cusp.

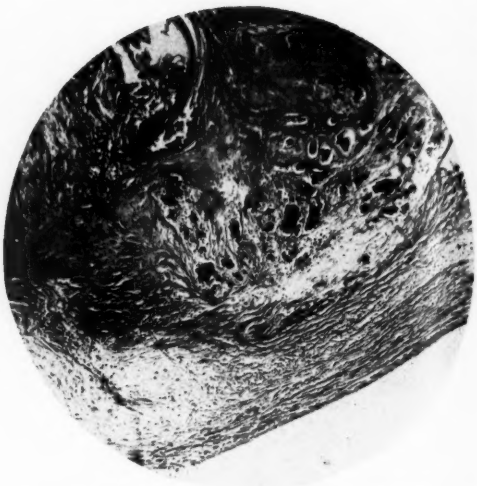

FIG. 4. Dog 5, hyalinization, cartilaginous metaplasia, and calcification near a silk suture at annular attachment of a homografted cusp.

in others only toward the attachments of the cusp to the papillary muscle and to the annulus, there occurred avascular replacement of fibrous tissue by cartilage and there were foci of amorphous material containing calcium (Fig. 4). In the transplanted papillary muscle and in the transplanted annulus these degenerative changes were uniformly found. A striking feature in all cases was the sound healing of the host tissues to the grafted tissue, and the invasion of a limited zone of the graft by blood vessels.

DISCUSSION

The failure of a homografted cusp to maintain its resilience after 6 months is obvious. There are 2 possible factors in this failure. In the first place the cavitary blood may not be sufficient to keep the graft healthy in the conditions of constant movement in which it is placed, and in the second place the degenerative changes may be those found in all homografted tissues.

In all reported experiments in which autogenous tissue has been placed within the heart cavities some degenerative changes have been found. Thus Wilson states that "microscopic examination revealed that the strip (of fascia, tendon, or parietal pericardium) became gradually compressed into a solid cellular cord with a covering of smooth endothelial-like cells." In Moore and Shumacker's series, inverted veins and arteries in ventricular cavities showed intimal proliferation, a structureless media and adventitia, and sometimes fragmentation and vacuolation. Tendons showed disappearance of elastic tissue and cartilaginous metaplasia, and pericardium showed central ischemic acellular degeneration with peripheral fibrosis.

The changes which occur in homografted tissues have been extensively studied in relation to the replacement of arterial defects. Peirce, Rheinlander, Moritz, Gross, and Merrill found in 7 dogs studied 1 to 9 months after insertion of a formalin-fixed homograft in the aorta that acellular degeneration of the media, sometimes with calcification, was accompanied by preservation of the graft elastica and the formation of a new intima and adventitia by the host. Nyhus, Kanar, Moore, Schmitz, and others, furthermore, observed the same changes in fresh and preserved aortic homografts in pigs.

Lam, Aram, and Munnell transplanted a segment of aorta containing the aortic valve from one dog into another. They found that after a time the grafted valve became functionless because of shrivelling of the valve cusps and thrombosis, although in a second series in which the host dog's aortic valve was first rendered incompetent, the results were better and nearly half the grafted valves looked fairly normal after several months.

There seems no doubt that arterial grafts are antigenic and no reason to doubt that valve cusp grafts are likewise. Until these two factors of antibody reaction and avascular degeneration are controllable, it is unlikely that tissues inserted into the heart chambers will survive and function.

Since this work was done a very similar investigation has come to the authors' notice. In this paper Robiczek claims that 14 of 16 dogs in which 1 tricuspid cusp had been homografted 1 to 22 months previously showed a competent valve on clinical, electrocardiographic, cardiac catheterization, radiographic, and autopsy examination. Photographs reproduced in this article do, however, show thickening of the cusp and, as he and his colleagues point out in another paper (4), hemodynamic effects are only noticed when 2 or more tricuspid valves have been removed. "The loss of one cusp is presumably compensated by the annulus fibrosus in a manner similar to that described for the mitral valve."

SUMMARY

In 10 dogs homografted tricuspid valve cusps healed to the host but soon lost their resilience, degenerated, and became nonfunctional.

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THE PATHOGENESIS AND IMPLICATIONS OF THE ELECTROLYTE IMBALANCE IN URETEROSIGMOIDOSTOMY

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THERE ARE THREE CONDITIONS which may require diversion of the urinary stream: exstrophy of the bladder, incontinence of urine, and carcinoma of the bladder necessitating cystectomy. There are others, for example, intractable fistulas, but these are less common.

In 1911, Coffey published a description of his method of ureterosigmoidostomy and in the ensuing 45 years more than 100 different operations were described for implantation of the ureters into the colon. There have been three major complications associated with this surgery: (1) obstruction with hydronephrosis occurs in 88 per cent of postoperative kidneys and results either from stricture formation at the site of anastomosis or from the greater colonic pressure of 270 centimeters of water exerted against a ureteral pressure of 35 centimeters of water; (2) there is the complication of pyelonephritis caused by continued fecal contamination; and (3) the metabolic imbalance—hyperchloremic acidosis. With diversion of the fecal stream by colostomy proximal to the ureterointestinal anastomosis, it is frequently possible to avoid both pyelonephritis and hydronephrosis. The electrolyte imbalance, however, is not so easily solved.

It is the purpose of this research to elucidate further the problem of hyperchloremia (Part I) and to demonstrate that the basic difficulty from colonic diversion is not only hyperchloremia, as commonly believed, but potassium depletion (Part II). It will be shown that the physician can be placed in a paradoxical therapeutic situation, in which the correction of the potassium imbalance may serve to augment the acidosis resulting from hyperchloremia. These latter observations, coupled with the insidiousness of potassium depletion and the inherent difficulties in measuring chronic loss of cellular potassium, may serve further to condemn the operation of ureterosigmoidostomy. Finally, the implications of similarities between cells of the intestinal mucosa and renal tubules in relation to current potassium-acid-base concepts are discussed.

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PART I. — THE PROBLEM OF HYPERCHLOREMIC ACIDOSIS

Hyperchloremic acidosis following ureterosigmoidostomy was first described by Boyd in 1931. Nearly 20 years elapsed before Ferris and Odel, based on a study of 141 patients, observed that the insertion of a rectal tube with prompt colonic drainage would reverse the progressive symptomatology of excessive thirst, weakness, anorexia, vomiting, diarrhea, coma, and Kussmaul breathing. This observation might have been inferred from earlier work by Jewett with animals. Ferris and Odel found 79 per cent of their patients had some degree of hyperchloremia, and 80 per cent were acidotic at varying intervals following ureterosigmoidostomy. Their observations on the effectiveness of rectal or nephrostomy drainage suggested chloride absorption from the bowel. As a result, a low salt diet with added sodium bicarbonate became the accepted treatment for nausea and acidosis accompanying ureterocolostomy.

Ferris and Odel called attention to the earlier work of Goldschmidt and Dayton in 1919 concerning studies on the mechanism of absorption from the intestine. These earlier publications, combined with the later

ones of Visscher, Ingraham, and Burns, constitute the most significant early experimental work on intestinal absorption. These studies demonstrated that rapid chloride impoverishment occurred from the ileum *or* colon when isotonic or even hypotonic solutions were placed in isolated segments. Visscher believed the process was selective, involved metabolic work on the part of the cells, and that the movement of chloride ions from gut to blood was 200 times that expected from simple osmosis.[1] Both Goldschmidt (24, 25) and Visscher (30) demonstrated the enhancement of chloride absorption by polyvalent anions, such as $SO_4^=$ and $PO_4^=$, which needs little emphasis when we recall the prevalence of phosphate anion in the urine, and that $PO_4^=$ excretion is further increased in acidosis. Visscher (56) pointed out that polyvalent anions may even inhibit the absorption of sodium from the gut, since the rate of migration of radioactive sodium from gut to blood was greater from isotonic sodium chloride than isotonic sodium sulfate, although the sodium concentration was greater in the latter solution. And so the basic physiology necessary for anticipating metabolic difficulties in ureterosigmoidostomy was performed 30 years before the clinical elucidation of the problem.

Following Ferris and Odel's clinical observations, the beautiful experiments of the English urologists at Leeds finally demonstrated the differential absorption of excessive chloride over sodium from the colon in the human. Pyrah's method (42) of a two stage cystectomy was admirably suited for elucidation of this problem. At the first operation, the left ureter is anastomosed to the sigmoid, and a proximal end colostomy performed above the anastomosis. This effects two separate urinary streams: the right renal urine passing normally to the bladder and out the urethra, while the urine from the left kidney first crosses the isolated rectosigmoid mucosa and out the anal sphincter. In patients in whom creatinine clearances were approximately identical from both kidneys, the chloride output from the rectum was consistently 60 to 80 per cent less than the excretion across the bladder, while the sodium from the rectum was less than that from the bladder by 60 to 74 per cent. In addition, when the left kidney was nonfunctioning (from previous renal obstruction), urine from the bladder was placed directly in the sigmoid pouch, and again, rapid reabsorption of chloride in slight excess of sodium occurred.

These experiments were then repeated (43), using radioactive isotopes, and a differential distribution was demonstrated in the blood stream, as well as the disappearance of more chloride than sodium from the rectal pouch. It is readily apparent that chloride uptake is only slightly in excess of sodium from the rectum (a repeated observation in their nonradioactive studies), and yet the increase of chloride over sodium in the blood stream is very striking. The authors attributed this to the greater "sodium space" in the body than "chloride space," and in a later paper (49) found that if equivalent amounts of labeled sodium and chloride are injected intravenously, the sodium in 60 minutes is distributed throughout 22 liters of body space, whereas chloride diffuses into 15 liters. It has been known for years that sodium has a cellular distribution, while chloride remains predominantly in the extracellular fluid, and that saline is acid to the extracellular fluids, since the chloride concentration of saline is 55 milliequivalents per liter greater than plasma chloride.

It would seem that hyperchloremia results not from any large amount of chloride absorbed from the gut in excess of sodium, but from the continuous and avid uptake of sodium and chloride ions practically milliequivalent for milliequivalent by the colonic mucosa—even *against* an osmotic gradient should diuresis place urine in the colon in isotonic or hypotonic concentrations. To be sure, there is a slight excess of chloride reabsorbed over sodium, but the primary source

[1] Whether the absorption is selective, as Visscher believed, or actually the effect of other ions is important enough from the point of general physiology, but the *net* absorption is the primary consideration here.

TABLE I

Date		Fluid intake, c.c.	Urine output, c.c.	Remarks	Urine placed per rectum, c.c.	Chlorides, mEq./L.	CO_2-comb. power, mEq./L.	NPN mgm. per cent	B.U.N. mgm. per cent	Na mEq./L.	K mEq./L.	Ca mgm. per cent	P mgm. per cent
Jan.	13				0.0	97.6	21.6	29.0		136.0	5.1	10.4	3.7
	14	1500	1460		400	102.8	26.6	54			4.9	10.5	3.5
	15	1220	510	All	410	102.0	24.2	35	20				
	16	1680	660	urine	660	108.2	24.2	40	20				
	17	1730	1245	replaced	1245	104.0	22.8	35	22				
	18	1680	1560	per	1560	103.0	19.9	33	19				
	19	1680	1150	rectum	1150	104.0	23.3	34	19				
	20	1680	900	q. 4 hrs.	875	102.0	24.2	30	18				
	21	1680	1085		935								
	22	1680	1180		920								
	23	1720	1545		1545	106.4	23.3	37	20				
	24	1720	1940		1940								
	25	1440	1940		1940	112.6	21.2	45	22				
	26	1440	2000		1450	112.2	17.4	43	27				
	27	1440	1800	300 c.c.	1100								
	28	1440	1475	Urine (maximum) replaced	875	108.6	22.5	46	28				
	29	1440	2185	q. 6 hrs.	1100								
	30	1440	1500		1150	106.2	25.0	40	24				
	31	1160	1740		1400								
Feb.	1	1200	2260		1800	114.0	23.3	46	37				
	2	1200	2075		1425								
	3	1200	1700	For remainder	1500	114.0	20.8	41	17				
	4	1150	2010	of study 300–350 c.c.	1910								
	5	1200	2450	(maximum)	1350								
	6	1200	1900	replaced	1450	109.0	19.1	40	25				
	7	1350	2050	q. 4 hrs.	1750								
	8	1200	2050		1950	112.4	18.3	47	29				
	9	1000	1890		1890								
	10	1060	1400		1325								
	11	1300	1350	Acid	1350	119.6	19.9	44	26				
	12	1290	1700	ash	1600								
	13	1530	1675	diet	1325								
	14	1250	1650		1600	110.4	18.3	51	31				
	15	1200	1385		1335								
	16	1200	1600		1600	118.0	17.4	44	29				
	17	1050	1525		1425								
	18	1200	1860		1860								
	19	1340	2000		1860								
	20	1070	1590		1490								
	21	1200	1660		1410	120.0	23.3	42	28				
	22	1350	1700		1500								
	23	1200	2035		1660	110.0	19.5	39	24				
	24	1280	1600		1500								
	25	1200	1700		1475								
	26	1200	1550		1500								
	27	1200	1350		1350	116.4	18.3	38	24	150.0	5.9		
	28	1125	1275		1075								
	29	1200	1450		1450								
March	1	1200	1560		1560	135.0	21.2	53	31	150.0	5.3		3.8
	2	*3160*	*2850*		No enemas	110.0	21.6	47	28	143.0	5.3		
	3	1000	1675	Urease	700 ??								
	4	1000	1375	added	600 ??								
	5	1250	1835	to	???	108.0	22.5	47	30	150.0	5.3		
	6	1050	1815	urine	600 ??								
	7	1200	1655		800 ??								
	8	1200	1875		???	109.6	19.5	47		147.0	5.1		
	9	1200	1500		Discont.								
	10	1150	1000										
	12					104.0	27.0	30		146.0	5.4		
	14					106.0	27.6	32		143.0	4.9		
	16	3645	1400										
	17	Discharged				100.0	28.4	33		143.0	5.2		

of acidosis is the milliequivalent for milliequivalent uptake by the bowel. The slight disproportion of chloride over sodium probably varies from patient to patient, and may be accounted for by the enhancement of chloride movement in the presence of phosphate anion. In the absence of salt restriction and added sodium bicarbonate, it is understandable why hyperchloremic acidosis is progressive: acidemia produces more phosphate excretion, which in turn, must intensify chloride absorption and serve to deepen the acidosis. There would seem to be little the body can do to prevent this progression, once acidosis is initiated. In effect, the plasma of patients with ureterosigmoidostomy receives a continuous infusion of saline, which is acid to the plasma by a variable amount slightly greater than 55 milliequivalents per liter of chloride ions. It will be shown that were it not for the fact that a concomitant potassium deficiency develops, many of these patients would have experienced a more severe acidosis.

In spite of the immediate acceptance of the chloride absorption theory in 1950, many observations remained unexplained. Why did some individuals develop hyperchloremic acidosis much later than others? And why did many patients have hyperchloremia, but no acidosis? For, it is a common finding to have elevated plasma chlorides and normal or only slightly depressed carbon dioxide combining power. When the plasma of patients who are asymptomatic is compared with the plasma of patients having severe symptoms, hyperchloremia is often as pronounced in one group as in the other. This fact is strikingly apparent in the two groups compared by Parsons, Powell, and Pyrah (42), although the authors made no comment on this observation.

There is the additional problem of why a few patients have a normal blood urea in the presence of hyperchloremia. Apparently, this observation has concerned some investigators, who have believed that osmotic forces are the only determinants of bowel absorption and have thus assumed that a high gut urea concentration should be in equilibrium with blood urea. Pendleton and West demonstrated in 1932 that urea accumulated in the intestine in greater concentrations than the blood, even when the blood urea was enormously increased, and Ingraham and Visscher (30) showed active ammonia secretion into the ileum as chloride was absorbed. When these studies are considered along with the polyuria forced upon the kidneys in patients with ureterosigmoidostomies, there are many possible explanations for normal blood ureas. Actually, this is a much overemphasized finding, as Jacobs and Stirling found hyperchloremia associated with a normal blood urea in only 9.0 per cent of 201 cases.

From these apparent discrepancies over the chloride absorption theory, an attractive and still current concept arose in 1951. Because a few patients develop hyperchloremia late[2] and since pyelonephritis and obstruction are common and often progressive sequelae to ureterosigmoidostomy, the suggestion was proposed that a specific renal tubular defect (secondary to pyelonephritis) was the cause of hyperchloremic acidosis. The evidence for this, which has been accepted, was essentially two-fold. Lapides first drew an analogy with the group of patients described by Albright and Reifenstein with hyperchloremic acidosis—the so-called "tubular insufficiency without glomerular insufficiency." Inasmuch as these patients have normal blood ureas (at least early in their clinical course), the analogy was apparently more attractive. To test this theory, that a tubular defect was necessary for the development of hyperchloremic acidosis, Lapides gave urine enemas to patients with normal renal function for periods varying from 6 to 12 days and could not cause a change in the serum electrolytes. The same experiment

[2]That this also is an overemphasized observation is shown by Jacobs and Stirling's analysis of 201 cases; 42.9 per cent had hyperchloremia 1 month after operation, 44.4 per cent at 1 to 6 months, and 48.6 per cent at 6 months and over. Since 35 per cent of these 201 patients were followed 2 to 3 years, and an additional 24 per cent followed 4 to 14 years after surgery, the rise in hyperchloremia between 1 month and years later is not impressive; 107 milliequivalents per liter were taken as normal for chlorides, rather than 103 milliequivalents per liter as used originally by Ferris and Odel.

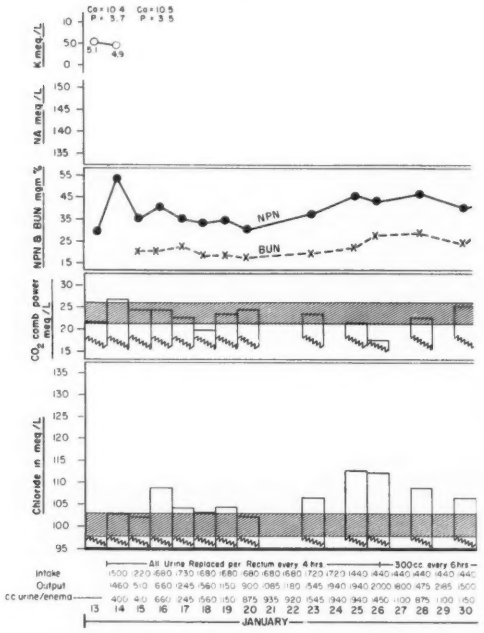

FIG. 1. The effect of urine enemas on serum electrolytes in the presence of normal renal function. The quantity of urine replaced by enema, and effectively retained by the patient per 24 hours is recorded as the lower row of figures (c.c. urine per enema).

was repeated in patients with severe obstructive uropathy, and hyperchloremic acidosis was reported. (Actually, in his study, the chloride of Patient A increased from 103 to 111 milliequivalents per liter while the acidosis lessened—the carbon dioxide combining power increasing from 25.9 to 27 milliequivalents per liter. Patient C's chlorides actually fell from a pre-enema level of 117 to 111 milliequivalents per liter, although the carbon dioxide combining power decreased from 15.4 to 13.6 milliequivalents per liter. Only Patient B exhibited an increase in chlorides from 105 to 110 milliequivalents per liter, while the carbon dioxide combining power fell from 18.1 to 16.8 milliequivalents per liter.) Thus, it seemed to Lapides that hyperchloremia could not be produced with normal renal function, and that a tubular defect similar to that described by Albright explained the elevated serum chlorides in the presence of a normal blood urea. Upon this analogy and this evidence is based the current theory that hyperchloremic acidosis indicates an underlying pyelonephritis. This allows the surgeon to believe that if normal kidneys can result from his particular method of ureterosigmoidostomy, metabolic imbalance need not be feared.

It is part of the purpose of this work to show that Albright's renal tubular acidosis is in no way related to the pyelonephritis of ureterosigmoidostomy, and that hyperchloremic acidosis can readily be produced in individuals with normal renal function. In addition, a few of the factors which influence the degree of hyperchloremia will be demonstrated, possibly explaining some of the variations.

PROCEDURE

H. G., a 59 year old white male, recovering from a plastic operation on his nose, developed difficulty on urination. On examination, he was found to have a moderate urethral stricture. After dilatation, a No. 18 Foley catheter was left indwelling. No residual urine was found, and urinalysis was negative for sediment. An intravenous pyelogram was normal, and the phenolsulfonphthalein excretion was 75 per cent in 2 hours, a value which is normal for our clinic. A urine concentration test was 1.032. Renal function, therefore was excellent.

Table I and Figures 1, 2, and 3 illustrate the results. Every 4 hours, day and night, the patient emptied his rectum, and the urine collected over the previous 4 hours was then given by enema at a slow rate for 30 minutes. The rectal tube was then removed, and the patient encouraged to remain in bed for 30 additional minutes. He was then allowed up and around the ward for the following 3 hours until time for the next enema. Except for the enemas, he was out of bed during the day, and slept 6 hours at night, but was awakened for his scheduled enema. His appetite was excellent, and he had no symptoms throughout the 9 weeks of study. He was an avid reader, and his mental acuity appeared not to change.

Weighing only 100 pounds, the patient's usual fluid intake was about 1,700 cubic centimeters per day. By the fourth day his urinary output was rapidly exceeding his intake, and fluids were restricted to 1,440 cubic centimeters per day, and then later to 1,200 to 1,300 cubic centimeters per day. This was necessary because he could tolerate only 300 to 350 cubic centimeters per rectum, and the restriction of fluids allowed a greater proportion of the total urinary output to be

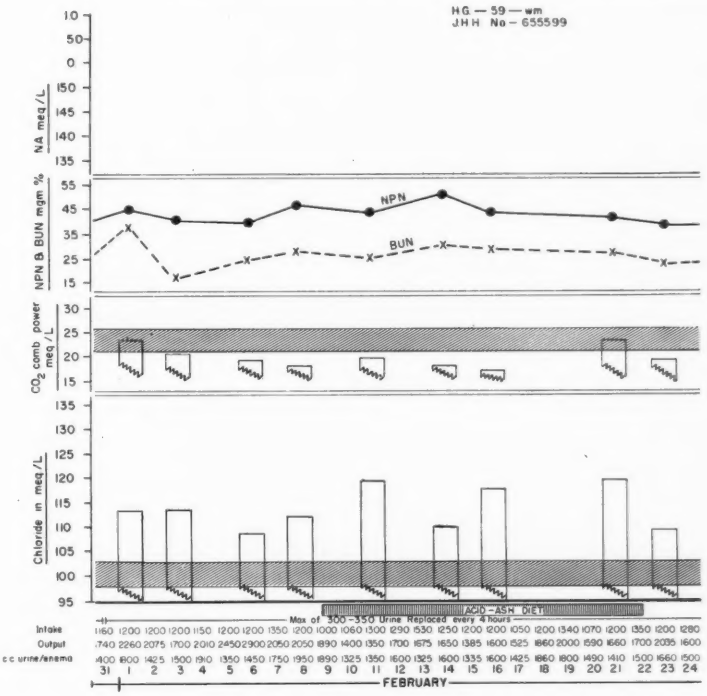

FIG. 2. Urine enemas (continued). The effect of an acid-ash diet

replaced. Because of the large reabsorption from the bowel, he was never dehydrated. His tongue was moist at all times, and thirst was not a complaint. Between January 26 and 31 he was temporarily placed on a 6 hour regimen, but this resulted in replacing too small a proportion of the total output. From January 31, until the termination of the enemas, the routine method of procedure was to replace the urine every 4 hours, but never to exceed 300 to 350 cubic centimeters at a single enema, and any remainder was, therefore, discarded.

Figures 4 and 5 demonstrate the wide distribution throughout the colon of a liquid which accumulates in the rectosigmoid, a finding often noted on intravenous pyelography in patients with ureterosigmoidostomy. What is not well appreciated is how ineffective rectal evacuation is for emptying the colon. Figure 4 was made 2 hours after the patient received a 300 cubic centimeter enema, of which 100 cubic centimeters had been replaced with 70 per cent urokon®. In Figure 5 is shown the roentgenogram which was made 2 hours later, immediately after evacuation in preparation for receiving the next scheduled enema. Even the appendix is filled in this postevacuation x-ray film, and it is obvious that only the sigmoid has been emptied of urine.

All electrolyte determinations were drawn before breakfast. It should be remembered that the fluid balances and urine enemas appearing on the chart on the same day as the chemistries, actually occurred for the most part after blood was drawn, and thus could not effect that day's electrolytes.

On January 13, the initial chemistries were uniformly normal. To measure the effect of dehydration, the patient was allowed nothing by mouth, and chemistries on the following day, January 14, showed his chlorides and carbon dioxide combining power had each increased 5 milliequivalents per liter. This 5 milliequivalents per liter range for carbon dioxide combining power and chloride is shaded on the charts as a normal variation for this patient. However, the 3 final carbon dioxide combining power determinations after conclusion of the rectal enemas would indicate that his average value is closer to 27 milliequivalents per liter than 21.6 milliequivalents per liter, thereby making the acidosis produced more profound than the shaded area would indicate. The nonprotein nitrogen rose during dehydration from 29 to 54 milligrams per cent, and this degree of increase is believed to be a laboratory error, since 3 nonprotein nitrogens at the termination of the study were 30, 32, and 33 milligrams per cent.

CONCLUSIONS REGARDING THE PROBLEM OF HYPERCHLOREMIA

The following conclusions seem warranted from this portion of the study:

1. It is possible to produce a profound hyperchloremia from urine enemas in the presence of *normal renal function.* Pyelonephritis is not required, nor is it necessary to postulate a specific renal tubular defect.

2. A mild, variable hyperchloremia was produced after 3 days of urine enemas, but 12 days were required for the more marked elevations of the serum chloride and depression of the carbon dioxide combining power.

3. The carbon dioxide combining power does not reflect the rise in chlorides milliequivalent for milliequivalent. High chlorides of 120 milliequivalents per liter were present simultaneously with a carbon dioxide combining power of 23.3 milliequivalents per liter. As already pointed out, this is a common finding in ureterosigmoidostomy, and the reason may be apparent when the potassium mechanism is discussed.

4. The effect of an acid-ash diet over an alkaline-ash diet is striking (Fig. 2). This patient preferred vegetables, and milk products, and was not an avid meat eater. Because of this, his dietary ash was decidedly alkaline (titrating to 26.0 c.c. of 0.1 *n* NaOH). When placed on a high protein, acid-ash diet (titrating to 38.0 c.c. of 0.1 *n* HCL), the serum chlorides reached 118, 119, and 120 milliequivalents per liter, and the average of carbon dioxide combining powers reached the lowest levels of the study. It would seem that dietary habits may partly explain the wide variation in the degree of hyperchloremia.

5. There was a persistent elevation of the nonprotein nitrogen and blood urea nitrogen during the time he was receiving urine enemas. (Normal nonprotein nitrogen for this laboratory is 22 to 40 milligrams per cent; normal blood urea nitrogen is 10 to 15 milligrams per cent.) This elevated blood urea nitrogen may indicate that gut urea absorption accounts for most of the elevated nonprotein nitrogen. However, it is impossible to rule out rapid conversion by the liver of HN_4^+ ion which may have been absorbed by the intestine and converted to urea. Work is needed on this problem.

6. Boyce and Vest first suggested that urea breakdown by urease producing bacteria in the colon might account for chloride absorption as ammonium chloride. That this mechanism is unnecessary, since most chloride is simply absorbed with sodium, has already been indicated. Nevertheless, as some chloride is absorbed in excess of sodium, the urease theory may play a minor role. To test this, the patient's urine was first demonstrated to be free of bacteria which split urea. Only coli-aerogenes was cultured (secondary to the indwelling catheter), and this organism did not split urea. Urease was then added to the bottle used for collecting the urine, and was present therefore throughout the 4 hour collection period prior to being replaced as an enema. The first urease enemas (Fig. 3) were started at 2 p.m., on February 27, continued through the next day, and on the following morning, March 1, the serum chlorides were 135 milliequivalents per liter! This result was checked twice by the laboratory. Although the nonprotein nitrogen and blood urea nitrogen reached their highest levels, the disturbing observation was the lack of change in the acid-base balance to compensate for the excess anion. The patient felt well, as usual, but the enemas were discontinued and fluids forced. As striking as this change seems, it is not intended to imply that the cause and effect are as direct as first appearance would seem. For one thing, the enemas were restarted the following day, and the results were disappointing. It is true that the patient's tolerance had reached the breaking point, and he was never again able to retain the enemas so completely. Nevertheless, enough urine was held at intervals during the closing 4 days that higher serum chlorides should have occurred. Furthermore, when a test was performed to measure the amount of urine urea decomposed by urease, the change seemed insignificant, urine urea

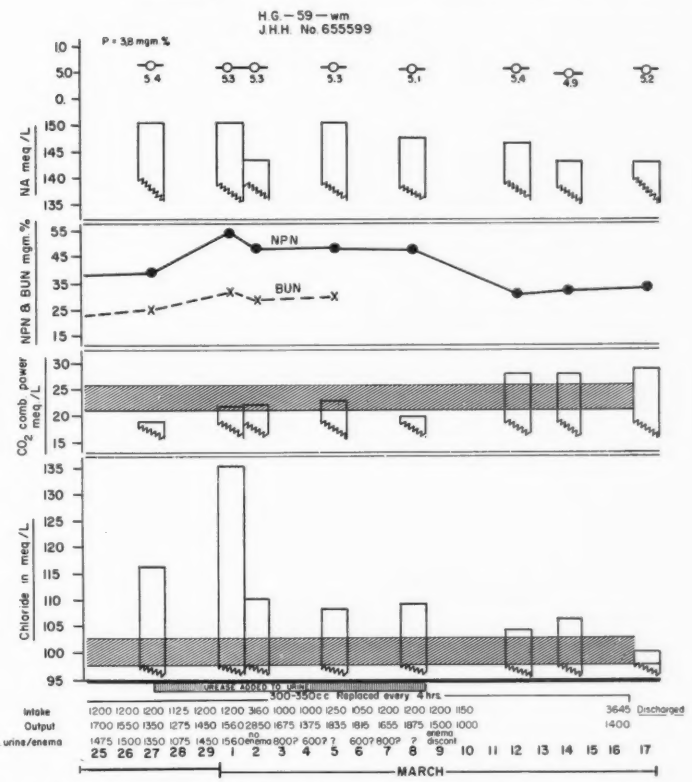

FIG. 3. Urine enemas (continued). The effect of urease. Enemas discontinued on March 9.

decreasing from 630 to 610 milligrams per cent after 4 hours of action by urease.[3] After the addition of urease to a quantity of the patient's urine, the *p*H changed from 5.0 to 8.0. From the work of Howell and Summer, this high *p*H, which is even higher when placed in the colon, is far from optimum for urease activity in the presence of phosphate buffers. It would appear that the role of urease in patients with ureterosigmoidostomy has been overemphasized, and except for producing an alkaline urine, is of little importance. But, if this is the case, we cannot explain the elevation of serum chlorides to 135 milliequivalents per liter.

7. The *p*H of the patient's urine, except during the addition of urease, was always strikingly acid, varying between *p*H 4.7 and 5.5. This is a finding emphasized by Parsons, Powell, and Pyrah (42), and is worthy of note. Alkalinity is a product of the colon, not of the renal tubules. Had this been realized, the analogy between Albright's patients with tubular damage could not have been seriously considered. Albright's hyperchloremic acidotic subjects not only have alkaline urines, but are unable to excrete acid. This is more than a quibble over a *p*H unit or two, because it is this very defect in ability to acidify the urine that is thought to explain the calcium loss and osteomalacia in Albright's patients, and it is the mechanism of potassium depletion. Interestingly enough, since many patients with ureterosigmoidostomies also lose potassium, equal confusion exists in the medical literature, and cases of

[3] Incubation of the 4 hour collection at 37 degrees C., instead of room temperature, made no difference in the amount of urea changed to ammonia nitrogen in the presence of urease.

FIG. 4. One hundred cubic centimeters of a routine 300 cubic centimeter urine enema was replaced with 70 per cent urokon®, and this x-ray film was taken 2 hours later.

ureterosigmoidostomies have been mistakenly included in reports on Albright's hyperchloremic tubular acidosis. Recognition of the highly acid urine in all ureterosigmoidostomies and chronic potassium loss in many ureterosigmoidostomies should avoid further misunderstanding.

8. Patients with diversion of the urine to the colon have an obligatory polyuria. A glance at the intake-output columns readily indicates that the urinary output was often double the intake. Ketwick first observed this when his patients, with the right ureter transplanted to the cecum and the left ureter in the sigmoid, could not reduce their output by restricting the fluid intake. The important question arises as to why this continual diuresis occurs. There are three possibilities: a water diuresis, an osmotic diuresis, or tubular damage with failure of reabsorption. The latter possibility is readily dismissed in this case because the kidneys were normal and the diuresis occurred early. However, as will be referred to later, potassium deficiency is a well recognized cause of renal damage and may not be so easily ruled out as a cause of polyuria in ureterosigmoidostomies. Reabsorption of water certainly occurs, but this is not a water diuresis since the specific gravity was approximately 1.018 to 1.020 whenever determined, and one chemical determination for urinary chlorides was 83 milliequivalents per liter. This obligatory polyuria would seem to be an osmotic diuresis. If this is so, simple calculations indicate the rapid rate at which chloride (and sodium) reabsorption from the colon must occur. Given a hyperchloremia of 117 milliequivalents per liter, and taking 102 milliequivalents per liter as the normal plasma chlorides, a 50 kilogram patient, who contains 10 liters of extracellular fluid, would have an excess of only 150 milliequivalents of chloride in his extracellular space. Assuming the moderate excretion rate of 75 milliequivalents per liter of chloride in the urine, 2 liters of urinary output should return the serum chlorides to normal. Therefore, the obligatory polyuria, being an osmotic diuresis, further emphasizes the dynamic turnover of large amounts of chloride, not so easily visualized in the more static uptake studies. The problem of an osmotic diuresis must be faced again when potassium loss is considered.

9. Finally, upon discontinuing the enemas, the serum electrolytes promptly returned to normal. From the few sodium and potassium determinations, the serum sodium slightly increased, and the potassium remained constant.

In concluding this portion of our work, one facet needs to be emphasized. The objection will be made that this method of replacing urine in the rectosigmoid does not simulate the conditions of ureterosigmoidostomy. It is not claimed that it does. Our primary purpose was to show the actual fact of hyperchloremic acidosis from contact with urine by the colonic mucosa in the presence of normal renal function. This has been shown. It is only a matter of degree as to

how close the conditions of ureterosigmoidostomy are actually approached. Certain it is that Lapides' method did not approach normal affairs with the patients remaining in bed, and the urine evacuated from the rectum every 3 hours by catheter outlet, avoiding the increased colonic pressure and fluid distribution during defecation. Furthermore, Figures 4 and 5 demonstrate the wide distribution of urine placed in the sigmoid as well as the ineffectiveness of evacuating the colon, and hence any method by which urine is experimentally placed in the sigmoid colon followed by defecation is valid as an approximation of actual conditions in ureterosigmoidostomies.

Part II. — The Problem of Potassium Depletion

The problem of potassium depletion in patients with ureterosigmoidostomy is not new. As the flame photometer came into more general use in 1950, isolated reports of potassium deficiency began to appear. The first of these was by Foster, Drew, and Wiss in 1950. Diefenbach, Fisk, and Gilson published a second case in 1951. More recently, Matern, Pyrah (48), Skanse and Widen, and in 1956 Loughlin have observed patients with potassium deficiency. No adequate explanations have been offered, other than to comment on its rarity or to suggest again the specter of Albright's tubular acidosis.

It is interesting that Korenberg inferred a possible potassium loss in 1951, apparently without even being aware of Foster's case the year before. This inference was drawn because Korenberg was impressed with the idea of saline absorption from the colon, deduced from the similarity in signs and symptoms between dogs receiving desoxycorticosterone acetate (DOCA) and patients with bilateral ureterocolostomy. He felt that potassium depletion might account for the weakness and weariness of patients, and referred to Mudge's work (41) on saline infusions causing cellular dehydration with loss of potassium. These deductions should not have been considered so lightly, as this is one of the mechanisms of potassium depletion.

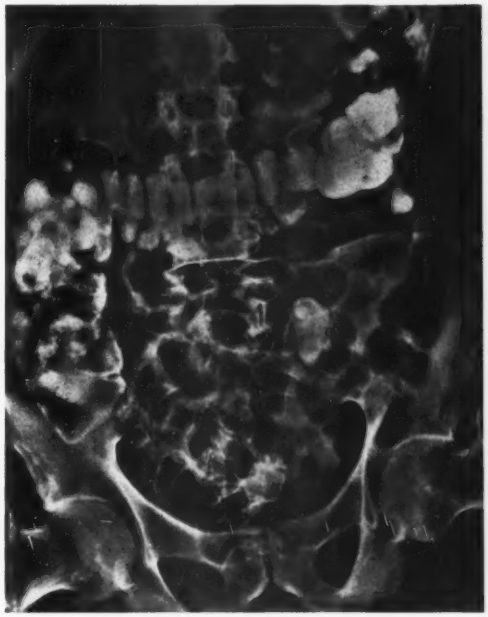

FIG. 5. X-ray film made 2 hours after Figure 4, immediately following evacuation of the colon.

Of equal importance to Korenberg's paper, was the report of Wilkinson in 1952. He first observed a patient who died of potassium insufficiency and followed this with a study of 6 additional subjects with bilateral ureterosigmoidostomy.[4] Four of these had low serum potassiums. He suggested that chloride was not the important imbalance, but potassium loss. Potassium loss was supposed to occur from "increased production and loss of lower intestinal secretions which are alkaline, and therefore [causes] a tendency to acidosis." From his studies, Wilkinson felt that his patients demonstrated such superb defense by the kidneys, that "the chemical alterations in the blood, far from indicating impairment of renal function, would have delighted Claude Bernard."

These latter two papers form an interesting contrast. They occurred about the same

[4] A brief look at these chemical determinations further illustrates the prevalence of hyperchloremia in the presence of a normal carbon dioxide combining power.

time; one was clinical, the other speculative. But more important is the fact that each touched a part of the problem to the exclusion of the other. Korenberg considered the potassium loss as solely secondary to salt reabsorption (except in terminal diarrhea), and Wilkinson would not accept the seriousness of sodium and chloride uptake from the colon—causing him to postulate an erroneous cause of the acidosis, and leaving him unable to explain Ketwick's obligatory polyuria.

The evidence for potassium loss in patients with ureterosigmoidostomies is impressive and occurs at two levels: (1) a cellular dehydration from the constant infusion of chloride and sodium which results in excessive renal excretion of potassium with the obligatory osmotic diuresis and (2) a constant washing from the colon of potassium, continuously secreted by the colonic mucosa.

THE RENAL LOSS OF POTASSIUM

It has been demonstrated in our patient that the obligatory polyuria, at least before potassium depletion occurs, is primarily an osmotic diuresis. This osmotic diuresis results not only from excessive chlorides, but from higher concentrations of blood urea. It was by urea infusion in dogs that Mudge (40) was able first to demonstrate potassium loss in the urine occurring in such excess over the amount filtered at the glomerulus that active potassium secretion by the renal tubules had to be considered. Furthermore, excessive chloride excretion with cellular dehydration causes potassium loss. A common observation is the potassium loss in patients receiving ammonium chloride.[5] Many experiments have shown the marked increase in potassium excretion resulting from cellular dehydration with movement of water and potassium out of the cells. One of the most effective ways to produce cellular dehydration is by saline infusion. The work of Mudge, Foulks, and Gilman (41) demonstrates that even without loss of cellular water, potassium excretion is enhanced by saline infusion, and when cellular dehydration occurs with hypertonic saline infusions, the loss of potassium increases tremendously. When we recall the dehydrated appearance of adult patients with ureterosigmoidostomy, the evidence summarized here for excessive chloride and sodium absorption, and the obligatory osmotic diuresis, there can be little doubt this constitutes one source of potassium loss.

[5]Similarities between patients receiving ammonium chloride and patients with ureterosigmoidostomies have often been commented upon.

THE COLONIC LOSS OF POTASSIUM

The evidence for a primary loss of potassium from the colon is equally impressive. Since a renal loss of potassium is continuously occurring, this colonic loss cannot be measured from renal urine perfusing across the colonic mucosa, unless a simultaneous measurement of potassium excretion at the kidney is obtained. The work of Parsons, Powell, and Pyrah (42) previously referred to regarding the absorption of sodium and chloride, is particularly interesting. These authors were not primarily concerned with potassium, and concluded with the statement "potassium excretions indicate that little, if any, was reabsorbed." Their figures indicate that if their potassium excretions are recalculated and expressed in milliequivalents per liter, rather than milligrams per 24 hours, in every case there is a significantly greater loss of potassium from the urine in the rectosigmoid. This could represent colonic loss, because regardless of how potassium excretion is increased at the renal level from absorption of chloride, urea, and sodium in the sigmoid mucosa, it must equally affect both kidneys. In addition, when 150 cubic centimeters of bladder urine were instilled into the rectosigmoid pouch (the left kidney being nonfunctioning from previous obstruction) 21.0 per cent more potassium was removed at the end of 2 hours. Assuming that the kidney was nonfunctioning, this difference would appear to be impressive, although the potassium increase may perhaps be explained by urine concentration from water loss.

Since the problem of water concentration could invalidate these conclusions, the experiments of Annis and Alexander are even more significant. Two patients with healthy colons below a descending colostomy had urine instilled into the isolated segment of rectosigmoid colon. Various ions were then measured for absorption after 3 hours of contact with the mucosa. Only their volume and potassium results are considered here, as they found the same rapid net absorption of chloride from the colon.[6] They concluded that in their Case 1 (constituting 3 experiments) there was no appreciable change in potassium concentrations. In the 2 experiments in their Case 2, the concentrations rose from 21 to 24 and from 33 to 44 milliequivalents per liter. These authors commented on the contrast between the behavior of sodium and potassium. However, when one compares the volume changes with the potassium concentrations before and after instillation, it is apparent that the differences are even more noteworthy. In every experiment, except in one experiment of Case 1, there was an increase in the volume of urine withdrawn over that introduced. This means that for the potassium concentration to remain the same, or even slightly increase, the actual net movement of ions must be greater than the concentrations indicate. Therefore, in every instillation, except the one experiment in Case 1 in which the apparent increase of potassium cannot be relied upon, there had to be removal of potassium ions from the colonic mucosa. In the last experiment of Case 2 the secretion of potassium is almost unbelievable for 3 hours of instillation.

That potassium secretion by the colonic mucosa is neither limited to stimulation from the presence of urine, nor represents a simple concentration phenomenon of previously introduced potassium, is amply demonstrated by infusion of saline into the isolated colon of the dog. D'Agostino, Leadbetter, and Schwartz placed saline in the

[6] It is interesting that in these studies the absorption of chloride was markedly greater than sodium, instead of almost milliequivalent for milliequivalent as in the radioactive studies by Parsons and associates previously referred to.

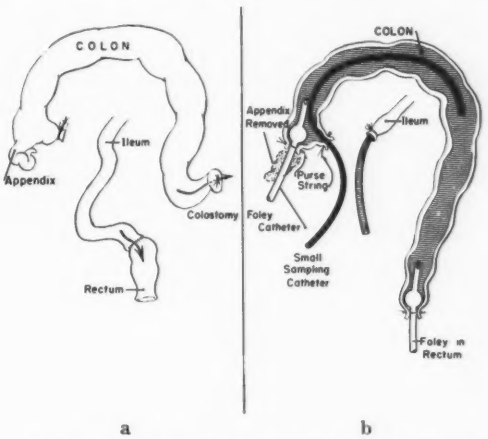

FIG. 6. Methods for studying electrolyte exchanges in the isolated colon of the dog: a, chronic experiment; b, acute experiment.

colon (which had been previously isolated from the fecal stream) of unanesthetized dogs, as in Figure 6a. As the chloride diminished, they found that bicarbonate ion increased, practically in the same proportions. But of far more importance was the observation that as sodium disappeared from the instilled saline, potassium increased almost milliequivalent for milliequivalent. Experiments were conducted over a period of 8 hours, and for sodium and potassium an equilibrium was established after 3 hours, with little change occurring throughout the following 5 hours. The sodium loss at equilibrium ranged between 15 and 45 milliequivalents per liter, while the potassium secretion varied between 15 and 20 milliequivalents per liter. This result demonstrates movement of potassium from the colonic mucosa to the lumen, and indicates that chronic depletion of this ion occurs in ureterosigmoidostomy not from hurried emptying of the ileum, but from a secretory exchange with the fluid contents of the gut lumen. This fact is all the more significant when we consider that the movement of potassium ions from mucosa to lumen in the presence of *urine* is occurring when the concentration of potassium is 4 to 6 times the concentration of plasma potassium. Even

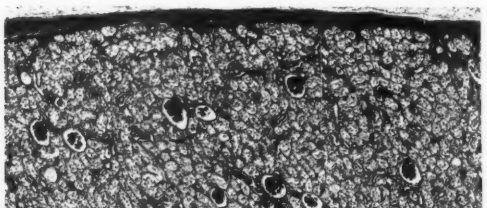

FIG. 7. Case 1. Kidney, 48 year old white female, 6 weeks postureterosigmoidostomy. Magnification, ×19.

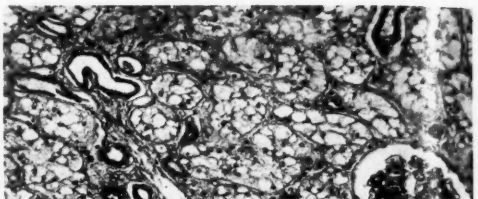

FIG. 8. Higher magnification (×95) of section shown in Figure 7.

from these few studies, the conclusion seems justified that the one mechanism whereby potassium loss might have been compensated for by reabsorption from the colon cannot occur at potassium concentrations usually present in urine. The perfusion studies of Pyrah and associates (49) in the human using isolated ileum seem to show that a net absorption of potassium occurs only when the potassium concentration is 3 times the serum potassium. The concentration of potassium in the *colon* necessary to effect net reabsorption over net secretion is unknown but the figures of Annis and Alexander would indicate that the level is much higher than 3 times. Initial experiments in dogs (55), using the preparation in Figure 6b, a modification of Goldschmidt and Dayton (21), suggest that net reabsorption of potassium does not occur from the colon even when isotonic concentrations of intracolonic potassium are 10 to 12 times the serum concentration of potassium. Furthermore, in ureterosigmoidostomies the effect of excess chlorides and other aberrations in the urine on potassium secretion are totally unknown. These latter abnormalities may even increase the required concentration of potassium in the lumen of the colon necessary to effect net movement from colon to blood. Be that as it may, at the usual concentrations present in normal urine, ureterosigmoidostomies can only lose potassium by secretion from the colonic mucosa. The determinants of these ionic movements and their magnitudes are obviously important but almost nothing is known about these exchanges. It is important not only from the cases under consideration here, but in infants with watery diarrhea, in patients with ulcerative colitis, and in electrolyte replacement in general.

THE PATHOLOGIC EVIDENCE FOR POTASSIUM DEFICIENCY

For those who prefer not to think in terms of ionic exchanges, there is further evidence of potassium depletion in individuals with ureterosigmoidostomies. For years, pathologists have noted occasional patients at autopsy with peculiar vacuoles in their renal tubules. Until quite recently the nature of these vacuoles had not been determined. In 1950, Kulka, Pearson, and Robbins reported 150 autopsied patients with various intestinal diseases (72 cases were ulcerative colitis) and found 15 instances of these giant vacuoles. These authors pointed out that small hydropic vacuoles, often multiple in a single cell and showing no tendency to displace the nucleus, were common in a variety of disease states. On the other hand, large solitary vacuoles, ballooning out toward the lumen, and seeming to press the nucleus

toward the base of the cell, were relatively rare. This latter vacuolar distribution was often patchy, filled the entire cytoplasm in one cell, and was frequently absent from the adjacent cell. Certain tubules were affected more than others. In occasional areas every cell was affected, and in others hardly a cell seemed involved. The process did not extend past the distal convoluted tubules. These large solitary vacuoles did not stain for glycogen or fat. In this report, in spite of a careful analysis of cases, no definite conclusion was drawn as to the cause of this vacuolar nephropathy.

The first proved case[7] of severe potassium deficiency associated with these vacuoles was published in the same year by Perkins, Peterson, and Riley. A patient with chronic diarrhea of long standing, whose serum potassium was 3.75 milliequivalents per liter and who had electrocardiographic evidence of potassium deficiency, died suddenly while receiving a 10 per cent glucose infusion. The renal tubules were identical with those that had so intrigued Kulka.

Keye reported a case in 1952 which will be of interest to physicians who attend patients with ureterosigmoidostomies. His patient had only 3 to 4 watery stools a day for 1 year and died abruptly while receiving 5 per cent glucose in saline. Ureterosigmoidostomies are encouraged to defecate oftener than 3 or 4 times a day. This was the patient's first infusion, and he was in good condition before the saline was started. At autopsy the renal tubular cells were filled with the same large, single vacuoles. We have emphasized earlier that saline infusion causes further potassium loss.

In 1943, Follis, Orent-Keiles, and McCollum reported renal vacuoles produced by potassium depletion in the rat.

Finally, Relman and Schwartz in 1955 reported 2 patients with chronic potassium depletion from self-induced diarrhea whose kidneys were biopsied and showed vacuolar tubular changes without glomerular or vascular disease. These patients had renal insufficiency. Repeat biopsies after partial potassium repletion showed "distinct evidence of healing." It is difficult to escape the fact that the peculiar vacuolar changes described by Kulka are intimately associated with potassium deficiency.

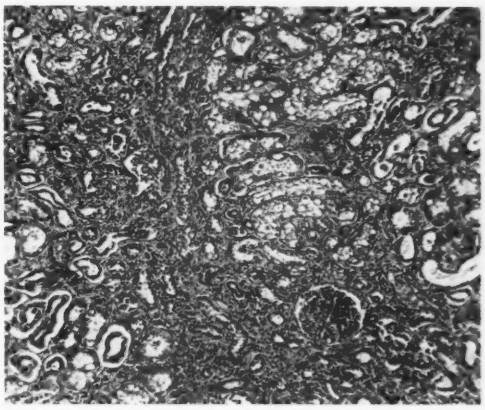

FIG. 9. Case 5. Kidney, 44 year old white female, 5 months postureterosigmoidostomy. Magnification, ×63.

Dr. Gerald Spear[8] and I have recently reviewed the renal lesions from 61 autopsies on patients who died with a ureterosigmoidostomy.[9] These include deaths in patients who had at least one ureter transplanted to the colon. Four cases of patients with a single ureter transplanted to the colon and the other anastomosed to the skin are included. Only 4 cases were excluded: 3 patients in whom bilateral nephrostomies were performed following transplantation of the ureters, and 1 patient who died following a Coffey II operation with both ureteral catheters still in place. These 4 cases did not have urine reaching the colon and are not included in the study. Seventeen of the remaining 57 patients (30 per cent) had typical vacuolar lesions in the renal tubules identical with those described by Kulka and associates, Perkins and associates, and Keye.

[7] The first reported case of low potassium associated with "clear cell nephrosis" occurred in 1947, but the authors (Williams and MacMahon) did not attribute the renal changes to the potassium deficiency.

[8] Department of Pathology.

[9] Attention was first called to the frequency of this vacuolar change in patients dying with ureterosigmoidostomy by Dr. A. R. Rich in a recent pathology conference on the renal lesion in hypokalemia.

Figures 7, 8, and 9 are representative sections.

Thirteen of the 17 cases were as severe as the 2 cases illustrated in Figures 7, 8, and 9. It is worth emphasizing that these findings are striking, and the sections chosen for illustration are typical of the 13 cases. The remaining 4 cases with vacuolar changes were easily identified, but were not as severe as those illustrated.

In the 17 cases with vacuolar change, the duration between transplantation and time of death varied from 7 days to 5 years, with most of the deaths occurring within the first year after surgery.

As would be expected, areas of pyelonephritis were more often present than not, but there were 3 or 4 cases in which infection was extremely minimal, and limited to rare areas containing a few acute inflammatory cells. In 1 of these cases there was no infection in the sections examined which were identical with those shown in Figures 7 and 8 throughout every field. It is interesting to record that this is Case 1, a 6 year old male exstrophy, previously reported in Doroshow's often quoted article published in 1951, in which he believed electrolyte imbalance, rather than pyelonephritis, was the cause of death. This confirms that thesis, but shows the death was basically potassium depletion with superimposed acidosis.

Figure 9 illustrates chronic pyelonephritis with vacuoles in adjacent tubules. It was not uncommon to find large areas of scar present with single tubules still functioning in the midst of the inflammation, but containing equally severe vacuoles. But as Kulka observed, the vacuoles vary not only from tubule to tubule, but from one cell to the next.

The nonprotein nitrogens prior to death ranged from 20 to 196 milligrams per cent.

It should be emphasized that these 57 deaths, except for the 4 cases in which urine probably did not reach the colonic mucosa, include all deaths between April 1920 and April 1954. The time interval between operation and autopsy was often very short (2 to 5 days), and potassium deficiency had little chance to develop. Early pulmonary emboli occurred in a few cases. Many of the deaths prior to 1945 were secondary to fulminating peritonitis from leakage at the anastomotic site, and life was often very short.

Only 2 of the 17 cases had serum potassium determinations. In 1 case the serum potassium varied from 3.1 to 3.6 milliequivalents per liter, and in the other case from 2.0 to 3.2 milliequivalents per liter.

A brief terminal history of a few of these 17 cases may be useful:

Case 1. A 48 year old white female was readmitted to the Gynecological Service on January 9, 1951. Six weeks previously a bilateral ureterosigmoidostomy had been performed. She suddenly developed progressive weakness, anorexia, paralysis, and loss of speech. Her reflexes were absent. Her nonprotein nitrogen was 137 milligrams per cent, the carbon dioxide combining power 5.6 milliequivalents per liter, and serum chlorides were 90.5 milliequivalents per liter. Death occurred 24 hours later while receiving an infusion of 5 per cent glucose in saline. Figures 7 and 8 are sections from this case.

Case 2. This 61 year old white female was admitted to the Medical Service with the presumptive diagnosis of myocardial infarction. A cystectomy and bilateral ureterosigmoidostomy had been performed 5 years previously. An electrocardiogram failed to show infarction. There were no chemical determinations. She died a few hours after admission on February 2, 1953. The heart was normal at autopsy. The renal tubules showed typical vacuolar nephropathy.

Case 3. This was a 55 year old white male admitted to the Urological Service for cystectomy and ureterosigmoidostomy. He was operated on May 25, 1949 and discharged 17 days later. A retropubic abscess necessitated readmission on October 26, 1949, and he was given a transverse colostomy. His nonprotein nitrogen was 45 milligrams per cent on October 26, 1949. He was admitted on February 10, 1950 for closure of the colostomy. He developed postoperative ileus, and the transverse colon was again brought to the skin. Thereafter he did well. On February 23, 1950, his nonprotein nitrogen was 51 milligrams per cent, chlorides 112 milliequivalents per liter, and carbon dioxide combining power was 13 milliequivalents per liter. While receiving an infusion of 1/6 molar sodium lactate, he suddenly died on February 23, 1950. Dr. Morgan Berthrong's conference note is interesting: "There are peculiar and very striking changes in the renal tubular epithelium, with large vacuoles in the cytoplasm of the convoluted tubules resembling fat. Sudan stains on frozen sections are negative. . . . The cause of sudden death is not clear from the autopsy

findings." The renal changes were identical with Figure 9.

CASE 4. A 53 year old colored female was admitted to the Gynecology Service, and a bilateral ureterosigmoidostomy with proximal colostomy was performed on April 29, 1953. She was discharged on the twenty-fifth postoperative day, but electrolytes on May 8, 9, and 14 had demonstrated low serum potassiums of 3.4, 3.6, and 3.6 milliequivalents per liter respectively. On discharge, her nonprotein nitrogen was 45 milligrams per cent, and chlorides were 106 milliequivalents per liter. She was readmitted on June 9 with the observation that she was "lethargic, speaks very slowly, and indistinctly." There was no history of vomiting. On June 9, her nonprotein nitrogen was 57 milligrams per cent, chlorides were 104.8 milliequivalents per liter, sodium was 133 milliequivalents per liter, carbon dioxide was 9.9 milliequivalents per liter, and the serum potassium was 3.1 milliequivalents per liter. The patient was weak and refused to eat. A psychiatric consultation was obtained on June 14 because of her refusal to eat. On June 16 her nonprotein nitrogen was 86 milligrams per cent, the carbon dioxide was 19.9 milliequivalents per liter, chlorides were 114.0 milliequivalents per liter, sodium was 133 milliequivalents per liter, and potassium was 3.6 milliequivalents per liter. She died quietly on June 17. At autopsy, her renal tubules were identical with Figure 9.

CASE 5. A 44 year old white female was admitted to the Gynecological Service and a palliative ureterosigmoidostomy was performed on September 17, 1948, with a wet colostomy. Following discharge she developed progressive weakness with only minimal nausea and vomiting. She was readmitted on February 13, 1949. Clinically she was not acidotic, respirations were not labored, but she was disoriented and hyporeflexic. Chemical determinations showed a nonprotein nitrogen of 90 milligrams per cent, a carbon dioxide combining power of 8.6 milliequivalents per liter, and chlorides of 122.3 milliequivalents per liter. She died 48 hours after admission. Figure 9 is a section taken from this case.

These cases are chosen at random, and the remainder of the 17 cases are no different. Progressive unexplained weakness, often ending in lethargy, anorexia, and a quiet death were all too often the common story. The symptoms too closely simulate terminal cancer for comfort, and there can be little doubt that many a patient who "gradually went down hill and died" would have gone up hill with a few milliequivalents of potassium. Stomach suction was not used on these patients, and vomiting was minimal to absent. It is clear, however, that gastric loss of potassium may be an additional source of depletion in the patients who died early in their postoperative course, or who experienced severe vomiting terminally. The progressive loss of appetite only serves to hasten the depletion.

In Ketwick's paper reporting 4 deaths in patients with the right ureter anastomosed to the cecum and the left to the sigmoid, he would not accept pyelonephritis as the necessary cause of electrolyte imbalance, because 2 of the patients did not have pyelonephritis. These two cases, however, did have "swollen, vacuolated" cells. Since hyperchloremic acidosis was equally present in both groups, as well as hydronephrosis, he was led to postulate that the vacuolated cells were secondary to obstruction, and that pyelonephritis was not necessary for hyperchloremia. With the latter belief this work is in hearty agreement, but the vacuoles are not produced by hydronephrosis. These patients died from potassium deficiency. His photomicrographs of the 1 case seem to show some autolysis, but there is little question that the vacuoles are identical to those in our cases. As a matter of fact, the serum potassium of this case was 3.3 milliequivalents per liter.

POTASSIUM DEFICIENCY AND RENAL INSUFFICIENCY

Although we do not know how much potassium can be lost before these vacuolar lesions appear, once they are present, there is little doubt of their effect. Potassium depletion per se causes renal insufficiency, in the complete absence of other glomerular or tubular disease. Schwartz and Relman (50, 53) have demonstrated not only the renal insufficiency of potassium depletion, but its reversibility after repletion of the deficient ion. It would seem reasonable that functional renal insufficiency appears before the pathologic changes, and a serious thought for physicians concerned with ureterosigmoidostomies is how much renal damage occurs from the potassium deficiency alone, which in many patients will be of more im-

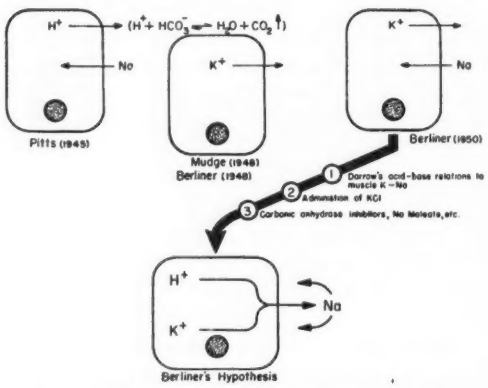

FIG. 10. Historical development of current potassium-acid-base concepts.

portance than the pyelonephritis. The combination of the two constitute a serious threat to life.

POTASSIUM-ACID-BASE RELATIONSHIPS IN PATIENTS WITH URETEROSIGMOIDOSTOMY

This concludes the evidence for potassium loss in patients with ureterosigmoidostomies. In this conclusion, however, resides the answer to several problems which have been hard to understand, and unfortunately, the demonstration of the difficult, if not paradoxical position of the physician who undertakes to correct the electrolyte imbalance.

Without some knowledge of the classical work performed over the past 10 years on potassium-acid-base relationships, a rational approach to the management of urinary diversion is difficult.

Figure 10 illustrates the basic work and observations that led to Berliner's thesis on the inverse relationship of potassium and hydrogen ions in the cells of the renal tubule. Pitts during 1945 to 1948 proved that active hydrogen secretion occurs in the kidney tubule, and the hydrogen ion secreted by the cell exchanges for the sodium ion which is reabsorbed from the lumen. The first diagrammatic cell in Figure 10 shows this, but more important, demonstrates the relation between hydrogen ions and bicarbonate ions which must constantly be remembered if the following discussion is to be understood: the higher the concentration of hydrogen ion whether in the lumen of the renal tubules, or in the serum, the less the concentration of bicarbonate ion, due to the conversion of bicarbonate to water and carbon dioxide. Thus, in highly acid urines, bicarbonate disappears, while in alkaline urines it appears in high concentration. In the serum, if a shift of hydrogen ions occurs from the cells to the extracellular fluid, the carbon dioxide combining power falls; but if the shift is the reverse, the serum bicarbonate (carbon dioxide combining power) rises.

The experiments of Mudge (40) and Berliner and Kennedy (4) made it plain that potassium was also secreted by the renal tubules. Berliner, Kennedy, and Hilton (5) were then able to show that secreted potassium ion must also, like hydrogen ion, exchange for sodium in the kidney. From the clinical observation that administration of potassium chloride changes urine from acid to alkaline, and from Darrow's (15) work demonstrating the rise in serum bicarbonate as the muscle potassium diminished, the hypothesis was proposed that potassium and hydrogen compete for the same mechanism in the cell. Thus, when potassium chloride was administered, potassium being in excess, the hydrogen ion concentration in the cell falls, the urine becomes alkaline, and bicarbonate excretion is increased by virtue of the fall in hydrogen ion in the urine. Berliner, Kennedy, and Orloff (6) tested this by inhibiting hydrogen ion secretion with carbonic anhydrase inhibitors, and found potassium secretion was markedly enhanced, as well as bicarbonate. Other means of alkalinizing the urine, for example the administration of sodium malate, were all found to increase the secretion of potassium by the renal tubule (3). When these experiments of reducing hydrogen ion concentration and thereby increasing the renal secretion of potassium were combined with the clinical observation that potassium depleted patients secrete a highly acid urine, even in the face

of a serum alkalosis, Berliner's hypothesis seemed well founded.

Nevertheless, it remained for Cooke and his associates in rat experiments, to demonstrate that not only does the hydrogen ion increase in the renal tubule during potassium depletion, but a shift of hydrogen ions from the extracellular space to other cells also occurs. This causes an extracellular alkalosis (the bicarbonate rises in the serum as the hydrogen ion falls) and an intracellular acidosis which explains why the alkalosis resulting from chloride and potassium loss in surgical patients on gastric suction will not respond to adequate sodium chloride replacement until potassium is administered. Only then will the serum alkalosis and highly acid urine revert to normal.

Figure 11 illustrates the changes in the body cells in general, the urine, and the plasma, when the concentration of potassium or hydrogen ion is raised or lowered. Below each cell is represented the method for bringing about the increase or decrease in the ion concerned. Except for the effects of increased hydrogen ion concentration, these various changes have been confirmed both in animals and man. They are predictable relationships, the understanding of which is a prerequisite for grasping the pathogenesis of electrolyte imbalance in patients with ureterosigmoidostomies. The writer is aware that some of the controversial evidence has been omitted, for example, the finding of Black and Milnes that in experimental potassium depletion in man, the urine became alkaline, instead of acid as would be expected from Berliner's hypothesis. Nevertheless, the changes depicted correspond closely to Schwartz's superb review of potassium and the kidney in late 1955 (52), and allowing for the evidence in acute experiments, represents the best approximation of what is known currently about potassium-acid-base relationships.

If potassium depletion occurs in an animal by dietary deficiency or DOCA administration, the serum bicarbonate rises. The identical changes occur in man. The potassium in the cells is replaced by extracellular sodium, and as Cooke demonstrated, hydrogen ion in addition. But the degree of extracellular alkalosis depends on what additional changes occur in the extracellular sodium and chloride. For instance, the alkalosis of gastric suction or prolonged vomiting is not only caused by potassium loss, but is made doubly worse by the greater losses of chloride than sodium. Darrow's infants with diarrhea (14), although depleted of 30 per cent of their body potassium, were acidotic on admission because of the loss of more sodium than chloride in their stools. This result would be expected from the evidence summarized here for the colon's greater affinity in reabsorption of chloride over sodium. Ureterosigmoidostomies are chronically acidotic because of the excess chloride absorbed in relation to sodium (even if milliequivalent for milliequivalent), and this acidosis may suddenly be further increased by the well recognized diarrhea that precedes acidotic collapse in these patients, just as Darrow's infants were acidotic against a fundamental tendency toward extracellular alkalosis because of the potassium loss, but it is masked by the greater sensitivity of the extracellular compartment to both chronic and acute changes in sodium and chloride. This ex-

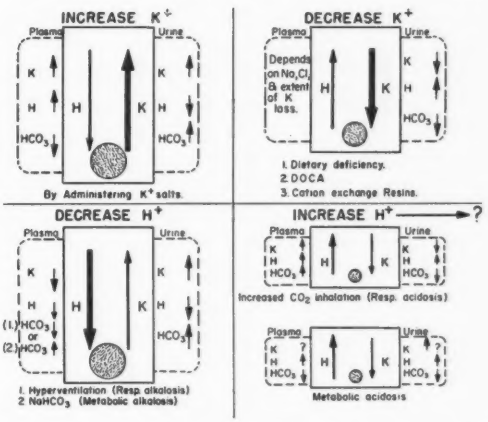

FIG. 11. The effect on the cell, the plasma, and the urine of increasing or decreasing potassium or hydrogen ions.

plains why so many ureterosigmoidostomies have hyperchloremia without a depressed carbon dioxide combining power for chronic potassium depletion increases serum bicarbonate. When the serum chlorides are high, and the carbon dioxide combining power has not decreased, hydrogen ion may have shifted intracellularly to replace part of the lost potassium, thereby artificially maintaining the carbon dioxide combining power of the serum.

The diagrammatic cell in Figure 11 shows the well documented changes from potassium chloride administration. It is the reverse side of the coin from potassium loss. This causes a fall in serum bicarbonate, and an extracellular acidosis, with an intracellular alkalosis. It is true that with the fall in hydrogen ion concentration in the urine, more bicarbonate is excreted, but Roberts, Magida, and Pitts have shown that this increase in urine bicarbonate is only one-third enough to account for the fall in serum carbon dioxide combining power. The remaining two-thirds probably occurs from hydrogen ions leaving the cells. Therefore, when we administer potassium to patients with ureterosigmoidostomies, we may further increase the serum acidosis.

The difficulty in treatment is now readily apparent. Since potassium loss has helped prevent a more serious acidosis, the correction of the potassium deficiency can make the acidosis worse. We have had occasion to observe a recent case which vividly demonstrates this paradox.

B. C., a 55 year old colored female, was admitted to the Gynecology Service in July 1955. A radical pelvic operation was performed on July 20, 1955, with bilateral ureterosigmoidostomies. Her Miller-Abbott tube remained in for 6 days, and for 4 of these days she received 2 grams per day of intravenous potassium chloride, and on July 25 sodium bicarbonate was begun. Nine days after surgery her nonprotein nitrogen was 22 milligrams per cent, chloride 104.0 milliequivalents per liter, carbon dioxide 24.2 milliequivalents per liter, sodium 134 milliequivalents per liter, and the potassium 2.3 milliequivalents per liter! Her gastric loss of potassium was adequately replaced since the drainage was minimal, but the renal and colonic loss probably represented several hundred milliequivalents, as the serum potassium will not usually fall this low unless considerable cellular depletion has occurred. She was discharged August 19, 1955, on sodium bicarbonate. Readmission occurred on September 29, 1955 because of chills, fever, nausea, and vomiting. Her nonprotein nitrogen was 24 milligrams per cent, carbon dioxide 33 milliequivalents per liter, chloride 94, sodium 143, and potassium 2.1 milliequivalents per liter. Some of the alkalosis was due to chloride loss from vomiting, but 2 weeks later, having received glucose and saline the first few days, the chloride was 107.6 milliequivalents per liter, carbon dioxide was 30.4 milliequivalents per liter, sodium 147.0 milliequivalents per liter, and potassium 2.6 milliequivalents per liter. She was discharged the following day and readmitted on November 8. The electrolytes on December 30 show the only serious attempt at replacement with potassium chloride and illustrate why that was abandoned: potassium was 4.9 milliequivalents per liter, carbon dioxide 12.4 milliequivalents per liter, chloride 104.0, and sodium 131 milliequivalents per liter. We were later able to show that potassium administration also lowered the serum sodium in this patient, the meaning of which is not clear, unless sodium is excreted with the chloride ion from the potassium chloride. A transverse colostomy was performed on January 13, 1956, and no change occurred in the electrolyte imbalance. However, on attempting to sigmoidoscope this patient, the reason for the severe electrolyte imbalance became clear. From previous pelvic adhesions, the sigmoid was angulated and strictured just above the rectosigmoid junction, so that the entire descending colon served as an overflow reservoir, causing enormous losses of potassium, and rendering ineffective rectal tube drainage. It is not hard to understand why a few of the autopsies with renal vacuolar nephropathy occurred soon after transplantation of the ureters.

POTASSIUM DEFICIENCY AND SODIUM BICARBONATE ADMINISTRATION

Further study of Figure 11 demonstrates what may be a serious difficulty with the current treatment of ureterosigmoidostomies. The administration of sodium bicarbonate is universally used in the correction of acidosis from the hyperchloremia, and is usually given prophylactically, as in the patient just reviewed. Nevertheless, in acute experiments, this method causes potassium loss. Animals can be made potassium-deficient by the administration of sodium bicarbonate and a low chloride diet, and dogs receiving intravenous 5 per cent sodium bicarbonate will increase their rate of potas-

TABLE II.—THE EFFECT OF SODIUM BICARBONATE ON THE URINARY EXCRETION OF POTASSIUM IN A PATIENT (B. C.) WITH BILATERAL URETEROSIGMOIDOSTOMY AND A TRANSVERSE COLOSTOMY

Date	Total Na intake, mEq./24 hrs.	K output in urine, mEq./24 hrs.	pH arterial blood	Salt diet gms.	Serum electrolytes: NPN mgm. per cent	CO_2-c.p. mEq./L.	Na mEq./L.	Cl mEq./L.	K mEq./L.	Ca mgm. per cent	P mgm. per cent
May 25	101.8	71.2		3							
27	101.8	71.3		3							
28	101.8	50.5	7.40	3	32	23.3	132	95.8	5.4	11.2	5.6
30	113.5	41.6		3							
31	256.3*	44.7		3							
June 1	256.3*	26.4		3							
2	256.3*	27.3		3							
3	256.3*	26.5		3							
4	238.5	33.3		11							
5	238.5	40.3	7.44	11	30	28.4	143	95.0	4.4	10.1	4.6
7	238.5	57.1		11							
8	238.5	53.3		11							
9	381.3*	55.8		11							
10	452.7*	38.5		11							
11	428.9*	34.1	7.40	11							
12					25	33.0	139	100.0	4.9	8.8	4.5

*Added sodium given as sodium bicarbonate.

sium excretion 15 fold. Sodium bicarbonate lowers the hydrogen ion concentration, extracellularly and within the cell, and as the hydrogen ion falls in the renal tubule cell, potassium secretion is markedly enhanced. So delicately tuned is potassium excretion to alkalosis in man, that 15 minutes of simple hyperventilation will raise the excretion rate of potassium from 87 to 266 microequivalents per minute.

Because these are acute experiments, and because sodium bicarbonate administration would not be expected to cause additional renal loss of potassium unless the hydrogen ion concentration was lowered, patient B. C. was further studied. It was first found that when her serum potassium was low, the 24 hour urine potassium would fall to levels of 6 milliequivalents per liter. The oral administration of potassium chloride lowered the carbon dioxide combining power markedly. Potassium gluconate was not as severe in this respect, but caused diarrhea. Potassium bicarbonate had no detectable tendency to lower the carbon dioxide combining power. She was best controlled by utilizing a mixture of potassium-sodium-citrate devised by Dr. J. E. Howard for alkalinizing the urine of certain patients with calculous disease. It consists of 1 milliequivalent of sodium and potassium per cubic centimeter, and this patient was best maintained on 10 cubic centimeters 3 times a day. When the serum and urine potassium had reverted to normal on this regimen, she was placed on a balance study to measure the effect of sodium bicarbonate on potassium excretion. Bowel losses were not measured (transverse colostomy), and although she had no diarrhea except for 1 day, this loss constitutes a regrettable unknown in the balance totals. Since a low salt diet is usually recommended along with sodium bicarbonate in patients with ureterosigmoidostomies, the effect of the alkali on potassium excretion was measured on both a low salt diet (3 grams) and a normal salt diet (11 grams). Hydrogen ion concentration determinations were made on arterial blood. Table II shows the results. The total amount of sodium received each day can be compared with the amount of potassium excreted in the urine per 24 hours. The patient was given a constant amount of potassium every day, 96 milliequivalents. These results show that potassium excretion in the urine was not appreciably affected by moderate doses of sodium bicarbonate. However, it has been demonstrated that larger doses of sodium bicarbonate and sodium citrate (775 milliequivalents of sodium per day) do increase the urinary loss of potassium and cause renal damage in healthy adults when administered for only 3 days. These latter amounts of alkali are so large

that the experiments probably approach the conditions of acute experiments referred to previously, in which there is no question that sodium bicarbonate causes further potassium loss. It will also be noted that in our results the *p*H of the arterial blood did not appreciably change.

Furthermore, if Berliner's hypothesis is true for cells other than those of the renal tubules (as Cooke's work indicated at least for potassium depletion), then sodium bicarbonate may also increase potassium secretion in the colon. However, the renal excretion is marked and all mobilized potassium may be handled by the kidney. In either case, Figure 6b offers a direct method which lends itself to testing if other cells in the body are behaving identically to the renal tubule cells in potassium-acid-base exchanges. Experiments are currently being performed to measure the acute effect of sodium bicarbonate on potassium secretion by the colon (55).

POTASSIUM EXCRETION IN THE PRESENCE OF A LOWERED HYDROGEN ION CONCENTRATION

Finally, since ureterosigmoidostomies tend toward acidosis, a complete understanding of potassium changes would entail accounting for the effects of raised hydrogen ion concentration. Information on this is difficult to obtain, because in producing acidemia secondary effects are initiated which in themselves cause potassium changes, and the effect of the hydrogen ion per se cannot be viewed with certainty. However, several acute experiments on respiratory acidosis indicate a fall in potassium excretion in the urine.

Summary and Conclusion

In conclusion, patients with diversion of the urine to the colon, regardless of how much colon is used or if only one ureter is transplanted, may lose potassium. The only requirement is absorption of chloride, sodium, and urea in quantities sufficient to initiate an osmotic diuresis. Local secretion of potassium by the colon is a second source of ionic loss. Pyelonephritis is not necessary for hyperchloremic acidosis or potassium loss. The problems resulting from performing an operation that may lead to chronic potassium loss in a large number of cases are not easily dismissed. This is particularly so in these patients because the hyperchloremia leads to a serum acidosis on the one hand, and the potassium loss causes a serum alkalosis on the other. The role of sodium bicarbonate in relation to potassium loss needs further elucidation.

But perhaps the greatest difficulty resides in the insidiousness of potassium deficiency. Although it causes renal insufficiency and may produce weakness, lethargy, and anorexia hardly distinguishable from terminal cancer, it is often a relatively asymptomatic disease. If potassium deficiency could be measured by serum determination, this might not be such a serious problem. But potassium is the major cation of the body, totalling some 3,000 to 4,000 milliequivalents, with only 70 milliequivalents present in the extracellular fluid. These 70 milliequivalents are notorious for not reflecting the level of body potassium, and may even be present in high concentrations when depletion is severe. The electrocardiogram reflects extracellular potassium,[10] and is thus subject to the same difficulties as the serum potassium. Muscle biopsies and balance studies will reveal the amount of potassium deficiency, but these are not easy to carry out, and certainly are not out-patient studies. If one of these patients should arrive at the hospital sick, dehydrated, and acidotic, the use of intravenous sodium bicarbonate or lactate, or 10 per cent glucose, will occasionally end in sudden death if the potassium deficiency is severe enough. Yet with dehydration, the serum potassium may not be low, and pyelonephritis being so common, the attending physician does not like to give intravenous potassium unless the urinary output is first adequate.

[10]Even in the severe potassium depletion of diabetic acidosis, the serum potassium may be high from dehydration and excessive potassium mobilization, and the electrocardiogram reflect a hyperkalemia—not the underlying and more serious potassium deficiency.

Finally, when prophylactic replacement of potassium is undertaken on an outpatient basis, it must be remembered that excess potassium will be excreted in a system which is singularly susceptible to reabsorption at some undetermined concentration in the colon. Who has the courage to risk the even greater danger of hyperkalemia with cardiac arrest in the presence of so many unknowns?

Except where rapid and continuous run-off of urine occurs from a short segment, the operation of ureterosigmoidostomy should probably be abandoned.

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CARCINOMA IN THE MEDIAL AND LATERAL HALVES OF THE BREAST

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PRIOR TO THIS TIME, all statistical studies of carcinoma of the breast reported from the Mayo Clinic have concerned themselves with the different grades of cancer and the presence or absence of axillary metastasis. As a result of recent interest in the problems of internal mammary chain involvement, superradical mastectomy, and also the basic question of what does and what does not constitute adequate surgical treatment of carcinoma of the breast, it was decided to review our material with these factors in mind.

MATERIAL AND METHODS

For the purpose of this study, the years 1947 and 1948 were arbitrarily chosen because a 2 year study would give a larger number of cases and a 5 year follow-up could be easily obtained.

Case histories of 650 patients indexed as having been treated surgically for carcinoma of the breast at the Mayo Clinic in 1947 and 1948 were found; on review of these histories, 223 of the cases were excluded from further consideration in the pathologic analysis for the following reasons: no residual tumor in the radical mastectomy specimen because of a previous biopsy before coming to the clinic in 58 cases; simple mastectomy only done in 19; more than 1 quadrant involved in 63; roentgen treatments before coming to the clinic in 7; recurrence after operation when first seen in 9; no palpable mass on examination in 21; not localized as to quadrant in 11; previous "paste" treatment in 3; axillary mass only in 1; bilateral simultaneous cancer in 3; simultaneous neurofibrosarcoma in 1; semiradical mastectomy done (simple mastectomy with axillary dissection or preservation of the pectoralis minor muscle) in 10; recurrence at the biopsy site done 6 years previously in 1; local excision of recurrence done for diagnosis only in 1; testosterone implanted in the rectus muscle in 11; simultaneous adenocarcinoma of the uterine fundus in 2; and intraductal papilloma in 2 cases.

Multiple microscopic sections on the remaining 427 cases were then reviewed, and 11 more cases were excluded from the study for the following reasons: melanoepithelioma of the chest wall in 1 case; lymphosarcoma in the breast after a previous diagnosis and treatment of lymphoblastoma in 1; not cancer when reviewed in 6; and sclerosing adenosis when reviewed in 3 cases.

After these eliminations, 416 cases in which carcinoma of the breast presented itself as a palpable mass for which radical mastectomy was done constitute the basis of this study. Of the patients, 414 were female and 2 were male. The average age for the total group of patients was 52.9 years. The right breast was involved in 221 cases and the left breast in 195 cases.

In order to localize the tumor into the various quadrants of the breast, the gross specimens removed at the time of operation and preserved in 10 per cent formalin were examined. The breast was divided into upper outer quadrant, lower outer quadrant, upper inner quadrant, lower inner quadrant, 3 o'clock, 6 o'clock, 9 o'clock, 12 o'clock, and central or subareolar positions.

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Based, in part, on the thesis submitted by Dr. Pierce to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

TABLE I.—DISTRIBUTION BY LOCATION OF LESION

Location	*No.*	*Per cent*
Upper outer	180	43.3
Lower outer	51	12.3
Upper inner	43	10.3
Lower inner	20	4.8
Central	34	8.2
3 o'clock	15	3.6
6 o'clock	10	2.4
9 o'clock	23	5.5
12 o'clock	40	9.6
Total	416*	100.0

*During the 2 years, 1947 and 1948, there were an additional 234 patients who had lesions that were not classifiable by location.

It was necessary to have these 9 distinct locations to localize the malignant lesions accurately and to cut down on the problem of overlapping, especially in the midzones between the various quadrants. As the examiner faces the patient, the tumor can be localized in a standard fashion, provided a clockwise route is followed on the left side and a counterclockwise rotation followed on the right when the examiner begins superior to the nipple at the midnipple line or in the 12 o'clock position. In this way, all 3 o'clock lesions, for example, will be in the lateral portion of the breast regardless of whether the right or the left side is under discussion (Fig. 1).

TABLE II.—TYPE OF MALIGNANCY CORRELATED WITH GRADE AND METASTASIS

Type	*Grade*	*Axillary node metastasis*	*Right*	*Left*	*Total*
Adenocarcinoma	1	Without	2	1	3
		With	0	0	0
	2	Without	14	5	19
		With	5	0	5
	3	Without	44	45	89
		With	50	31	81
	4	Without	34	29	63
		With	48	56	104
	Total	Without	94	80	174
		With	103	87	190
		Total	197	167	364
Comedocarcinoma	1	Without	1	4	5
		With	0	0	0
	2	Without	5	4	9
		With	0	0	0
	3	Without	6	7	13
		With	2	2	4
	4	Without	3	3	6
		With	1	3	4
	Total	Without	15	18	33
		With	3	5	8
		Total	18	23	41
Paget's disease		Without	4	3	7
		With	1	2	3
		Total	5	5	10
Liposarcoma			1	0	1

RESULTS

Table I shows the distribution of the lesions within the various quadrants. Our distribution agrees with the distributions of earlier writers. The largest number of lesions in any one location was found in the upper outer quadrant. The next most frequent site was the lower outer quadrant and so on.

Of the 180 lesions in the upper outer quadrant, 160 were found to be adenocarcinomas on microscopic examination, 18 were comedocarcinomas, and the remaining 2 were Paget's disease of the breast. One hundred and one were localized within the right breast and 79 in the left breast. There were only 2 grade 1 adenocarcinomas and 4 grade 1 comedocarcinomas. However, 19 were grade 2 lesions, 78 were grade 3, and 75 were grade 4. Eighty-eight of the 180 cancers in this quadrant had metastasized to the axilla by the time of operation, giving a frequency of 48.9 per cent.

Only 15 lesions were found in the 3 o'clock position. Of these, 13 were adenocarcinomas, and 2 were comedocarcinomas. The right breast was involved in 3 and the left breast in 12 of the cases. No grade 1 lesions were present in this quadrant. There were 2 grade 2, 6 grade 3, and 7 grade 4 cancers in this location. Nine of the 15 patients (60 per cent) had positive axillary nodes in the radical mastectomy specimen.

The lower outer quadrant was involved in 51 cases. Thirty-nine lesions were adenocarcinomas, 9 were comedocarcinomas, 2 were Paget's disease, and 1 was a liposarcoma. The latter was the only liposarcoma in this group of 650 surgically treated carcinomas of the breast. Twenty-three lesions were located in the right breast and 28 in the left breast. No grade 1 lesions were found in this quadrant. There were 6 grade 2, 18 grade 3, and 24 grade 4 cancers localized to this area. Metastasis to the axillary

nodes was found in 17 of the surgically resected specimens, giving a rate of 33.3 per cent.

From the 6 o'clock position, 10 cancers were removed. In 6 cases a right, and in 4 cases a left, radical mastectomy was performed for 8 adenocarcinomas, 1 comedocarcinoma, and 1 instance of Paget's disease. No grade 1 lesions were found, but 2 grade 2, 5 grade 3, and 2 grade 4 lesions were found in this location. In 5 of the 10 cases (50 per cent) there were positive axillary nodes.

Twenty cancers were found in the lower inner quadrant, with 10 of them on the right and 10 of them on the left side. Seventeen adenocarcinomas and 3 comedocarcinomas were examined. There were no grade 1 or 2 lesions in the lower inner quadrant, but 10 grade 3 and 10 grade 4 lesions were present in the surgical specimens. Seven of the 20 (35 per cent) had metastatically involved the axillary nodes at the time of operation.

Twenty-three cancers were located in the 9 o'clock position. Twenty-one of these were adenocarcinomas and only 2 were comedocarcinomas. Eighteen had been removed from the right and 5 from the left breast at the time of radical mastectomy. There were 2 grade 1 lesions but no grade 2 lesions in this location. The remainder was made up of 11 grade 3 and 10 grade 4 lesions. At the time of operation, of the 23 cases localized to this quadrant, 14 (60.9 per cent) had metastatically involved the axillary nodes.

Forty-three lesions were located in the upper inner quadrant. Of these, 40 were adenocarcinomas, and 2 were comedocarcinomas. There was a single case of Paget's disease in this area. Twenty-four lesions were in the right and 19 in the left breast. None of this group were found to be grade 1 lesions. However, 3 were called grade 2, 22 grade 3, and 18 grade 4 cancers. Twelve of the 43 (27.9 per cent) had metastasized to the axilla.

Forty cancers were localized to the 12 o'clock position. There were 39 adenocarcinomas and 1 comedocarcinoma. The right breast was involved in 22 and the left breast in 18 cases. No grade 1 or 2 lesions were found. However, 24 of this group were classified as grade 3 and 16 as grade 4. Axillary nodes were found to be positive for cancer cells in 26 of the 40 cases (65 per cent).

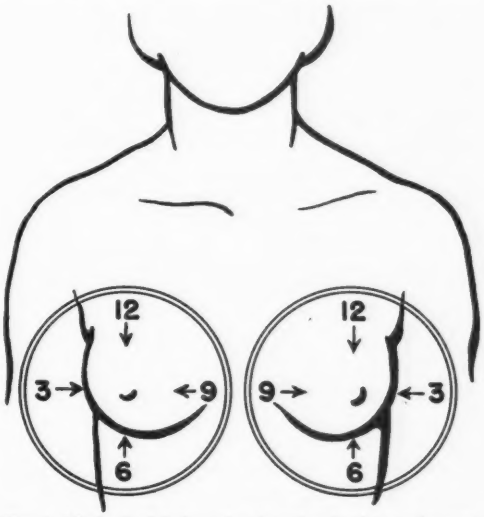

FIG. 1. Method of designating location in the two breasts.

There were 34 cancers confined to the central or subareolar portion of the breast. Twenty-seven were adenocarcinomas, 4 were Paget's disease, and only 3 were found to be comedocarcinomas. Fifteen of these had been in the right and 19 in the left breast at the time of operation. No grade 1 lesions were found. There were 1 grade 2, 13 grade 3, and 16 grade 4 lesions in this location. At the time of radical mastectomy, 23 of these 34 lesions (67.6 per cent) had metastasized to the axillary nodes. An aggregation of the pathologic findings without the tedious breakdown previously described is shown in Table II.

The next problem was to consolidate these lesions into medial and lateral halves. Arbitrarily, it was decided to incorporate the upper outer quadrant, 3 o'clock, lower outer quadrant, and 6 o'clock subdivisions into the lateral half. The medial half was then, of course, composed of lesions occupying the lower inner quadrant, 9 o'clock, upper in-

TABLE III.—DISTRIBUTION OF LESIONS AFTER CONSOLIDATION OF QUADRANT LOCATIONS

	Patients	
Location	*No.*	*Per cent*
Medial half	126	30.3
Lateral half	256	61.5
Central	34	8.2

TABLE IV.—INCIDENCE OF METASTASIS BY LOCATION

	Total	*With metastasis*	
Location	*patients*	*No.*	*Per cent**
Medial	126	57	45.2
Lateral	256	122	47.7
Central	34	23	67.6
Total	416	202	48.6

*Per cent of patients with metastasis in this location.

ner quadrant, and 12 o'clock positions. The central or subareolar portion was kept separate and made the third major division in this classification. Table III shows the results of this consolidation.

In Table IV, the incidence of metastasis has also been consolidated in this manner. The over-all 48.6 per cent incidence of positive axillary nodes is somewhat lower than the over-all Mayo Clinic experience of 60 per cent, but this discrepancy is probably due to exclusion of diffuse and inflammatory lesions, since these could not be localized within a single quadrant. In inflammatory carcinoma of the breast, for example, Meyer and associates have shown that the axillary nodes were metastatically involved in all cases reviewed by them at the Mayo Clinic, and the prognosis for this group of patients is very poor, with only 6 per cent living more than 5 years from the time of operation.

The remaining 234 patients surgically treated for carcinoma of the breast during the years 1947 and 1948 which could not be localized to a single quadrant have not been entirely ignored in considering the over-all 5 year survival rate for carcinoma of the breast. Table V shows that this group had a 58.9 per cent 5 year survival rate.

TABLE V.—FIVE YEAR SURVIVAL RATES BY LOCATION

	Patients		*Lived 5 years or more after operation*	
Location	*Total*	*Traced*	*No.*	*Per cent**
Medial	126	126	74	58.7
Lateral	256	251	158	62.9
Central	34	33	18	54.5
Total	416	410	250	61.0
Not localized	234	224	132	58.9
Total	650	634	382	60.3

*Based on traced patients. Inquiry as of January 1, 1955.

Of the 416 patients studied in detail, 410 were traced (Table V). A 5 year follow-up examination was obtained in 98.6 per cent of this group of patients treated surgically for carcinoma of the breast.

In the group of patients with tumors localized to the medial half of the breast who underwent radical mastectomy in 1947 and 1948, 58.7 per cent survived for 5 years or more after operation. In the group of patients with lesions in the lateral half of the breast, 62.9 per cent survived 5 years or more from the time of operation. The central group had 54.5 per cent surviving for 5 years or more from the time of radical mastectomy. The over-all 5 year survival for the group of 410 traced patients was 61.0 per cent. It is interesting to compare this group with the smaller group of 234 patients previously excluded because of inability to localize their tumors to a single quadrant. In this latter group we were able to trace 224 of the patients and found that 58.9 per cent survived 5 years or more from the time of operation. Therefore, for the total of 650 patients treated by radical mastectomy for carcinoma of the breast during 1947 and 1948, we were able to determine that 60.3 per cent survived 5 years or more from the time of operation.

A further subdivision was then done and, as is shown in Table VI, the 5 year survival rate was determined on the basis of not only the presence or absence of axillary metastasis but also of location of the lesion as originally found in the diseased breast.

Five year survival rates were also determined for lesions within each of the 9 arbitrarily determined anatomic subdivisions of the breast. However, because of the small numbers in certain of these locations, it was believed that this further subdivision, even though it might show a trend, would be

TABLE VI.—FIVE YEAR SURVIVAL RATES BY LOCATION AND AXILLARY METASTASIS

	With metastasis				*Without metastasis*			
	Patients		*Lived 5 years or more after operation*		*Patients*		*Lived 5 years or more after operation*	
Location	*Total*	*Traced*	*No.*	*Per cent**	*Total*	*Traced*	*No.*	*Per cent**
Medial	57	57	26	45.6	69	69	48	69.6
Lateral	122	121	51	42.1	134	130	107	82.3
Central	23	22	8	36.4	11	11	10	90.9
Total	202	200	85	42.5	214	210	165	78.6

*Based on traced patients. Inquiry as of January 1, 1955.

more likely only to add to the confusion of small numbers and be of no significance statistically.

When Table VI is analyzed, we see that only 45.6 per cent of the patients with tumors in the medial half of the breast who had positive axillary nodes at the time of operation were alive 5 years or more from the time of radical mastectomy. It is of interest to compare the figures for the lesions located in the lateral half of the breast. Here 42.1 per cent of the patients survived 5 years or more from the time of operation. This survival rate is not statistically different from the survival rate for lesions of the medial half. Of the patients with central lesions, 36.4 per cent survived 5 years or more after operation.

With a similar breakdown of the groups without axillary metastasis, we find that 69.6 per cent of patients with lesions of the medial half survived for 5 years or more from the time of operation. In those cases in which the lesions were located in the lateral half of the breast, the 5 year survival rate was 82.3 per cent. The difference of the latter 2 survival rates may be of some significance. It could indicate that a number of the medial lesions had metastasized to the internal chain without having involved the axillary nodes. However, this is merely speculation, since there was no means of studying internal mammary node involvement in this group of cases. Under similar circumstances of negative axillary nodes with a medial lesion, Handley and Thackray reported that in 6 of their 61 cases (9.8 per cent) metastasis to the internal mammary chain had occurred. Under the identical circumstances, Dahl-Iverson found 4 of his 20 cases (20 per cent) with involvement of the internal mammary chain. Hutchinson, on the other hand, had only 1 in his group of 20 cases with positive internal mammary nodes from medial lesions when the axillary nodes were negative. Thus the extremes varied from 5 per cent, as in the latter instance, to a high of 20 per cent of metastatic involvement of the internal mammary chain when the axillary nodes were found to be free of metastatic involvement.

Though small, the central group of carcinomas without axillary nodal involvement demonstrated 90.9 per cent of patients surviving 5 years or more from the time of operation.

The over-all 5 year survival rate of 42.5 per cent for those patients with carcinoma of the breast and positive axillary nodes compares favorably with the figure of 32.5 per cent reported earlier by Harrington. The 78.6 per cent over-all 5 year survival for carcinoma of the breast without axillary nodal metastasis in this series is comparable to the 78.3 per cent reported by Harrington.

COMMENT

It is noteworthy that, although there was little difference in the 5 year survival rate of all patients having lesions of the medial and of the lateral halves of the breast, a difference was apparent in the group without demonstrable axillary nodal metastasis. The 5 year survival rate for patients without these metastases and with lesions in the medial half of the breast was 69.6 per cent, whereas with lesions in the lateral half it was 82.3 per cent.

An interpretation of the significance of these findings is difficult, since it is not known that the differences would pertain in another group of cases or in a larger series. At present, this finding can only be accepted as a true difference. The therapeutic implications must be considered.

Two additional facts are of interest. During the 2 years covered by this study, there were no operative deaths in this group of patients undergoing radical mastectomy. During this period, 86.4 per cent of all patients seen with carcinoma of the breast underwent operation.

The criteria of operability employed have been published by Harrington.

SUMMARY AND CONCLUSIONS

1. Four hundred sixteen cases of carcinoma of the breast were studied in detail. Three hundred sixty-four were proved to be adenocarcinomas, 41 were comedocarcinomas, 10 were Paget's disease, and a single case of liposarcoma was encountered.

2. The distribution in location of the tumors is given. The upper outer quadrant was the most frequently involved site (43.3 per cent).

3. Thirty and three-tenths per cent of the carcinomas were located in the medial half of the breast, and 61.5 per cent were located in the lateral half of the breast. The remaining 8.2 per cent were central in location.

4. The 5 year survival rate for the entire group was 61.0 per cent, that for lesions of the medial half was 58.7 per cent, that for lesions of the lateral half was 62.9 per cent, and for the central lesions was 54.5 per cent.

5. There was a 5 year survival rate of 58.9 per cent in the group of 234 patients whose lesion was not localized to a single quadrant but who nevertheless were treated by radical mastectomy during 1947 and 1948.

6. Patients who had lesions located in the medial half of the breast and with axillary metastasis had a 5 year survival rate of 45.6 per cent. Without axillary metastasis, the 5 year survival rate was 69.6 per cent.

7. Patients who had lesions located in the lateral half of the breast and with axillary metastasis had a 5 year survival rate of 42.1 per cent. Without axillary metastasis, the 5 year survival was 82.3 per cent.

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EDITORIALS

SUBPHRENIC ABSCESS

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EARLY RECOGNITION of a subphrenic abscess is difficult. Even before antibiotic therapy eliminated or altered the most significant clinical findings, exploration of the subphrenic spaces was often unwisely postponed.

The widespread and sometimes indiscriminate use of all of the antibiotics with resultant resistant mutations of bacteria, particularly the Staphylococcus aureus, has made the diagnosis and treatment of subphrenic abscesses even more difficult.

Unexplained fever, leucocytosis, and malaise a week or so after an abdominal operation, especially after contamination of the peritoneum, suggest subphrenic abscess formation. Pain and tenderness over the level of the tenth rib are compatible with involvement of the posterior superior space beneath the diaphragm. If x-ray and fluoroscopic examinations establish that the diaphragm is elevated or fixed, surgical exploration is indicated. Visualization of a fluid level beneath the diaphragm is virtually diagnostic, and associated pleural effusion is common. These are the time-honored, preantibiotic criteria of the diagnosis of subphrenic abscess. If all or a combination of these signs and symptoms are present, surgical intervention is justifiable.

These same diagnostic features are still valid, but it is important to compare the timing and severity of the signs and symptoms of subphrenic abscesses in the patient protected or overprotected with antibiotics. Fever is absent or low grade. Usually the leucocyte count and pulse rate are normal. Not infrequently, the patient's condition seems so satisfactory that he is discharged from the hospital. Weakness and malaise are considered consequences of the operation recently performed. However, the weakness, poor appetite, and lack of a sense of well being may result in compounding the therapeutic felony. The antibiotic treatment may be carried on at home and often a new drug is added. Sometimes there results a "shotgun blast" designed to eliminate all bacteria known to man.

The attenuated subphrenic abscess may remain relatively dormant for weeks or even months. Perforation of the abscess through the diaphragm into the pleura has occurred.[1] The resistant Staphylococcus aureus is the common pathogen and is usually somewhat sensitive to chloromycetin. Once an abscess is present, however, adequate surgical drainage offers the only cure.

Since early clinical manifestations of abscess formation are minimal, roentgen examination of the upper abdomen and lower thorax becomes particularly important. Air beneath the diaphragm may not be diagnostic shortly after a laparotomy, but persistence or increase of the air bubble requires surgical intervention.

Most of the calamities of morbidity and mortality resulting from the misuse of antibiotics in cases of subphrenic abscess could be avoided. There is no question that abscess formation sometimes can be prevented by

[1] GERWIG, W. H., and BLADES, BRIAN. The subphrenic abscess: a necessary re-evaluation. Ann. Surg., in press.

proper antibiotic therapy. In cases of perforated ulcers, appendiceal perforation, and other examples of gross contamination of the peritoneum, serious complications have been sharply reduced by a combination of antibiotic therapy and surgical intervention. It is equally true, however, that once an abscess is formed, drug therapy only masks the clinical manifestations and invites eventual disaster.

Whether routine postoperative antibiotic protection is advisable or even permissible is debatable. In the case of perforation of a viscus or of other circumstances resulting in the soiling of the peritoneum, antibacterial drugs are of the utmost importance. The antibiotics may abort the formation of a localized collection of pus. If, however, there is evidence of persistent localized abscess, surgical drainage is mandatory.

STAFF REPRESENTATION ON HOSPITAL GOVERNING BOARDS

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A QUESTIONNAIRE recently circulated to Fellows of the American College of Surgeons by a committee of its Board of Governors suggests that there is general increasing concern about staff representation on the governing boards of our hospitals. Reasons for this are probably related to several changing situations, among which are: (1) more hospital administrators who are not physicians, (2) stricter controls on expenditures, especially for personnel, and (3) more requests from general practitioners for appointments to hospital staffs and for operating privileges. With these changing conditions, many staff members have become afraid that their interests and those of their patients may not receive proper consideration by the administrator and governing board, usually none of whom are physicians, and they therefore believe that the staff should have adequate representation at the highest level of control.

Logical as this concept may seem, it will bear careful analysis and objective consideration. Let us consider the reasons for existence of the governing board, the procedures for qualifying and appointing governors or trustees, and the responsibilities and authority vested in them, and then decide whether or not active staff members are eligible to serve on the Board. Before the details relating to the Board of Governors are considered, it might be well first to review the reasons for establishment of a hospital and its relations to the community, the patients, and the medical staff.

Most hospitals are built and equipped with funds derived from taxation or individual donations and are dedicated to the care of the community's sick and injured. Their primary function is not to serve physicians nor are hospitals donated to physicians to be directed and controlled by them. Since the community contributes the capital funds for construction of a hospital to serve its people, its investment can be best protected by appointment of representative citizens to the governing board to administer the dedicated funds for the purposes indicated. The Board of Governors or Trustees is usually appointed by the agency that provides the funds for construction. The agency may be governmental (city, county, or state), religious, or voluntary. The governing board is charged with the responsibility of safeguarding the public's investment and the patients' interests and is cloaked with the necessary authority to pursue these ends. Such authority includes enforcement of high standards of patient care and appointment of an administrator and members of the medical staff. The governing board should be composed of a cross section of competent business and professional people who are sincerely interested in the hospital and willing to devote the time necessary to solve its problems. Furthermore, no board member should stand to profit by his position; otherwise he could not be expected to render unprejudiced or disinterested opinions on all questions considered.

Eligibility of staff members for appointment to a governing board can now be considered against this background. Staff physicians can qualify as competent citizens with sincere interest in the hospital and time to devote to its problems, but do they stand to profit personally by their positions on the Board? Numerous questions requiring decisions by the Board are concerned with general staff interests and certain ones may be of great personal concern to any staff member who might be on the board. Many such examples might be cited, among which are

consideration of staff promotions, selection of chiefs of services, priority on operating schedules, dismissal of staff members for cause, and selection of new staff members. Staff members on a governing board undoubtedly would have an opportunity to influence decisions in favor of themselves personally or the staff as a whole. Many physicians who might serve would doubtless be unselfish and objective in their considerations, but some would press their personal interests. The governing board that included staff members would be open to justifiable criticism from the public and other staff members, especially when decisions involved such matters as acceptance or dismissal of staff members.

Probably few who advocate staff representation on the governing board would recommend that the majority be staff members. The idea usually advanced is that one or two staff members should be included on the Board to make sure that the staff's viewpoint and interests are always presented fairly, and although these might influence decisions, they could not control them. Such minority representation actually constitutes only another plan for liaison between board and staff that would be substituted for the Joint Conference Committee that is accepted by most hospitals. A Joint Conference Committee, as recommended by the Joint Commission on Accreditation of Hospitals, is a standing committee appointed by the staff president that "shall consist of members of the active medical staff who will represent the medical staff in meetings with the governing body of the hospital or a committee of that body. This committee shall be a medico-administrative liaison committee and the official point of contact among the medical staff, the governing body and the administrator." Committees of this type have been functioning in well organized hospitals throughout the country for many years. Wherever such committees are active and alert, good liaison is maintained and the staff usually is quite satisfied. Staff dissatisfaction with board decisions usually results either from a committee that is not alert or from one with which the staff does not co-operate.

Obviously, the effectiveness of the Joint Conference Committee depends upon the willingness of its staff members to keep in touch with all staff activities and also with the deliberations of the governing board and the hospital administrator and to confer frequently and frankly with the other half of the committee that represents the governors. True liaison between staff and administration can be accomplished as well or better by this plan than by having one or two staff members sitting on the governing board.

THE SURGEON AT WORK

SURGICAL MANAGEMENT OF DISEASES OF THE SPLEEN

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OUR PURPOSE is to report some of our experiences with splenectomy for diseases of the spleen. Splenectomy for trauma, or to facilitate other surgical procedures, is not included.

REPORT OF CASES

Hereditary Spherocytosis

A white female, aged 20 years, presented herself with complaints of fatigue, shortness of breath, and a feeling of depression. Significant past history included frequent episodes of jaundice and attacks of epigastric pain. Family history was remarkable in that 7 of 9 siblings had been jaundiced. Physical examination was normal except for a palpable spleen without lymphadenopathy. Hemogram revealed 8.6 grams of hemoglobin; 3,380,000 erythrocytes; 14,800 leucocytes, with 45 per cent lymphocytes, 2 per cent monocytes, 53 per cent neutrophils, 1 per cent eosinophils, and 1 per cent basophils. A fragility test showed hemolysis to begin at .50 and to be complete at .44. Cold agglutination titers were negative. A special blood smear demonstrated marked variation in the size of the erythrocytes with polychromatophilia and spherocytosis. A splenectomy was performed. The removed spleen weighed 1,000 grams and was slate gray in color. The gallbladder contained multiple stones but was not removed. Microscopically, the spleen showed a prominent pale zone of medium and large lymphocytes around the malpighian corpuscles (Fig. 1). The spleen was packed with red cells, not in the sinusoids, but in the pulp. The specimen showed no free pigment or hemosiderin.

Following splenectomy the patient recovered without further appearance of jaundice. Blood studies on 3 occasions revealed the hemoglobin to vary between 12 and 13.4 grams, red blood cells to be 4,650,000, and white blood cells 9,200 and 12,000. The differential count was 40 per cent lymphocytes, 8 per cent monocytes, 47 per cent neutrophils, 4 per cent eosinophils, and 1 per cent basophils. Blood smears showed the presence of spherocytes. One year following the splenectomy the hemolysis in hypotonic salt solution began at .50 per cent and was complete at .44 per cent.

We believe this to be a case of hereditary spherocytosis with a favorable result following splenectomy. The postoperative findings of spherocytosis and increased fragility of the red cells to hypotonic saline solution will probably persist. The patient is clinically asymptomatic, and she has refused cholecystectomy.

Essential Idiopathic Thrombocytopenic Purpura in Pregnancy

A white female, aged 33 years, 5 months pregnant, had been bleeding from the mouth for 4 months. Recently, there had been petechiae of the skin. The bleeding had been severe enough to require transfusions elsewhere. There was no previous history of bleeding nor of exposure to toxic agents. Physical examination demonstrated petechiae and purpuric lesions on the mucous membrane of the mouth. There were many ecchymoses over the skin. The liver and spleen were not palpable. The uterus was felt 2 fingerbreadths above the umbilicus. The initial laboratory examinations showed: Urine negative except for microscopic red blood cells; hemoglobin 9.2 grams; red blood cells 3,370,000; hematocrit 36 per cent; white blood cells 9,000, of which 51 per cent were lymphocytes, 4 per cent monocytes, 45 per cent neutrophils with 3 band forms. The sedimentation rate was 82 millimeters (Westergren) in 1 hour. The reticulocyte count was 0.25 per cent, and platelet counts varied from 70,000 to 25,000. The bleeding time was 1 minute, 30 seconds; coagulation time 4 minutes, 40 seconds; prothrombin time 100 per cent. Hemolysis of the red blood cells began at .48 per cent and was complete at .38 per cent hypotonic saline solution. The clot retraction was not complete at the end of 24 hours. Bone marrow studies revealed an abundance of megakarocytes with poor platelet formation.

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FIG. 1. Photomicrograph showing a prominent pale rim of medium and large lymphocytes surrounding the malpighian corpuscle. Magnification of spleen in hereditary sperocytosis, × 65.

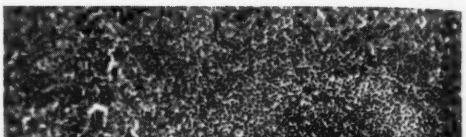

FIG. 2. A prominent pale zone around the periphery of the malpighian corpuscle of dense, medium, and large lymphocytes. Magnification of spleen in essential thrombocytopenic purpura, × 65.

The patient was prepared with cortisone which resulted in a reduction in the time for clot retraction but without change in the platelet count. Splenectomy was done, removing a spleen of normal size. There was a gradual return to a normal platelet count within 1 week following splenectomy. The clot retraction time returned to normal.

This is a case of essential idiopathic thrombocytopenic purpura which is somewhat unusual in that it occurred during pregnancy. McElin is of the opinion that splenectomy should be done for the preservation of the mother and the infant Both survived in this case, and no other pregnancies have occurred. We report this case because of the rarity of this problem. Results from conservative management, by and large, have been disastrous. No adverse effect on the pregnancy from the use of the cortisone was noted.

Primary Essential Idiopathic Thrombocytopenic Purpura

A male, aged 50 years, gave a 1 month history of constricting pain across the back and hemoptysis. Initial examination revealed a normal hemogram and sedimentation rate but an elevated blood uric acid. Roentgenograms of the chest and lumbar spine were all normal. Empiric therapeutic measures did not influence the symptoms. Three months later the patient developed a hypochromic anemia, and the platelet count was 70,000. Thorough x-ray examinations revealed only an obstruction of the right ureter with a nonfunctioning kidney on the same side. Bone marrow aspirations revealed megakarocytes with qualitative changes compatible with idiopathic thrombocytopenic purpura. The bronchoscopic examination was normal. Total plasma proteins were normal.

A splenectomy was done, the spleen being of normal size. No other abnormalities were found in the abdomen except a very firm adherent mass approximately 1 inch in diameter which was constricting the ureter at the pelvic brim on the right side. This could not be biopsied or removed through the incision for the splenectomy. The postoperative course was complicated by atelectasis, hemoptysis, and genitourinary tract bleeding, resulting in urinary obstruction by clots of blood. There were no changes in the laboratory findings following splenectomy. Cortisone did not affect the platelet count. The patient expired apparently from a subarachnoid hemorrhage. Autopsy was refused.

This probably represents a case of essential thrombocytopenic purpura in which splenectomy was of no value. No opportunity was afforded to examine the mass in the right pelvis.

Essential idiopathic thrombocytopenic purpura is characterized by exacerbations and remissions. Physical findings are submucous hemorrhages, intracutaneous petechiae, and spontaneous bleeding. The spleen is rarely palpable. Typical laboratory findings are reduced or absent platelets, nonretractable clots with prolonged bleeding time, normal coagulation time, and bone marrow containing normal or increased number of megakarocytes which may have qualitative abnormalities.

Anemia, Primary Neutropenia, and Possible Thrombocytopenia

A white female, aged 69 years had an anemia of 14 years' duration. Recently a troublesome diarrhea had occurred. Physical examination revealed a large spleen and liver. Red blood cells were 3,130,000; hemoglobin 9.5 grams; white blood cells 3,450, of which 70 per cent were neutrophils, 25 per cent lymphocytes, 2 per cent mononuclears, 2 per cent eosinophils, and 1 per cent basophils. The hemogram repeated 7 days later was the same. The bone marrow

was compatible with a diagnosis of pernicious anemia. Reticulocyte counts before liver administration were 3.4 and 3.8 per cent. The patient was treated with liver extract and vitamins. No cause for the diarrhea was found. Several months later the physical examination was unchanged. Splenic aspiration showed marked hyperplasia of the reticular cells lining the sinusoids of the spleen. Intervening pulp appeared to be more cellular than usual, most of the cells apparently being of lymphocytic origin. There was no evidence of hematopoietic activity of the spleen. The pathologist thought there was a possibility of hypersplenism, and preservation of the normal architecture ruled out a diagnosis of lymphoma. Repeated hemogram was 11 grams of hemoglobin, 3,750,000 red blood cells, 1,550 white blood cells, 56 per cent neutrophils, 36 per cent lymphocytes, 2 per cent mononuclears, and 6 per cent eosinophils. Subsequent white blood counts were 2,500 and 3,000. The patient was given 2 transfusions of whole blood. Three months later she still complained of weakness and diarrhea. Blood count revealed no significant change. A splenectomy was done, the spleen weighing 700 grams. Postoperative platelet counts varied between 70,000 and 250,000. The white blood cell count rose to 6,000 with a normal differential. The red blood cell count was 4,250,000 at the time of discharge. The patient improved symptomatically. Four years later the patient was still living, taking a liver preparation, and was much improved.

We consider this to be a case of hypersplenism with neutropenia, possible thrombocytopenia, and anemia. Microscopic appearance of the spleen demonstrated a prominent pale zone of medium and large lymphocytes surrounding the malpighian corpuscles and was not otherwise remarkable. There was no evidence of extramedullary hematopoiesis in the spleen. Bone marrow seemed adequate, and there was no absolute contraindication to removing the spleen. She has been improved as a result of the splenectomy.

Agnogenic Myeloid Metaplasia

A white female, aged 63 years, was followed for 5 years with a splenomegaly diagnosed as Banti's syndrome. This diagnosis had been made previously at a large medical center. Splenectomy had been advised at that time but was refused. At the time of final admission, the physical examination revealed a large spleen which filled at least one-third of the abdomen. The liver was palpable. The hemoglobin was 9.1 grams, red blood cells 3,000,000, white blood cells 8,350. The differential count was: lymphocytes 29 per cent, monocytes 8 per cent, neutrophils 48 per cent, eosinophils 4 per cent, basophils 2 per cent, and band forms 9 per cent. The peripheral blood smear showed polychromatophilia, anisocytosis, and poikilocytosis. The sternal bone marrow revealed only peripheral blood and unfortunately was not repeated. Although the anemia had been progressive for 5 years, interpretation of the peripheral smears had been unchanged. The platelet count was 240,000. The cephalin flocculation, bromsulphalein, and total plasma protein, were normal. Splenic aspiration revealed blood with an occasional myelocyte and late erythroblasts which, in retrospect, should have contraindicated splenectomy.

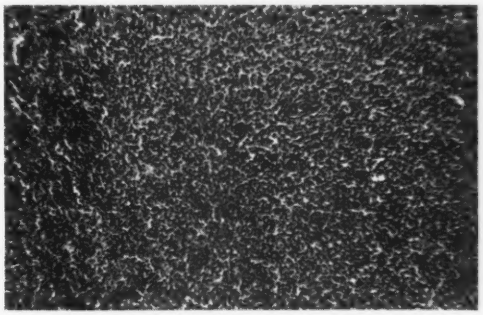

FIG. 3. The slide is of a low power showing tremendous splenic follicles. Magnification of the spleen in Hodgkin's disease, × 65.

A splenectomy was done, the spleen weighing 600 grams. The patient made an uneventful convalescence and was discharged from the hospital on the tenth postoperative day. The microscopic appearance of the spleen presented characteristic megakarocytes, and the cells throughout the sinusoids were erythroblasts and normoblasts. Six weeks after the operation she was readmitted to the hospital with a severe gastrointestinal hemorrhage. Multiple petechiae were present over the body. The platelet count was 9,000. The patient expired, and autopsy was refused.

This case is one of agnogenic myeloid metaplasia, or extramedullary hematopoiesis, or osteitis fibrosa. The splenic aspiration should have helped us in making a correct diagnosis. The spleen showed rather active hematopoiesis involving the platelets and red blood cells. We consider this an unfavorable result from splenectomy.

Hodgkin's Disease

A white male, aged 53 years, complained of a 22 pound weight loss, anorexia, and night sweats. Two weeks previously he had noticed a lump in the left side of the abdomen. Physical examination revealed a large mass in the left upper abdominal quadrant which was considered to be an enlarged spleen. The hemoglobin was 14 grams, red blood cells 4,400,000, white blood cells 4,450 with 37 per cent lymphocytes, 3 per cent monocytes, 59 per cent neutrophils, and 1 per cent eosinophils. One month later the hemoglobin was 12.6 grams, red blood cells 5,510,000 white blood cells 10,000 with 50 per cent lymphocytes, 2 per cent monocytes, 41 per cent neutrophils, 1 per cent eosinophils, and 6 per cent band forms. Platelets were 9,000. Sternal marrow aspiration showed hyper-

plasia of all the normal elements. Peripheral blood smears were essentially normal except for the decreased number of platelets. The sedimentation rate was 5 millimeters per hour, and bleeding and coagulation times were within normal limits. Total plasma proteins were normal. Splenic aspiration was done, and study of the aspirated material was believed to indicate a possible malignant lymphoma. Splenectomy was done and a spleen weighing 2,500 grams was removed. At the time of exploration a few small lymph nodes were found in the splenic pedicle, but no other lymphoid enlargement was noted in the abdomen, and the liver was normal. The platelet count climbed to 900,000 postoperatively and then gradually returned to normal. Six months postoperatively the hemoglobin was 13.6 grams, red blood cells 4,900,000, white blood cells 3,000, with a normal differential. The patient was seen occasionally without complaint. Three years after the splenectomy his hemoglobin was 6.6 grams, red blood cells 2,690,000, white blood cells 41,000, with lymphocytes 10 per cent, monocytes 13 per cent, neutrophils 71 per cent, eosinophils 2 per cent. There were 3 per cent band forms and 1 per cent myelocytes. The peripheral blood smear showed a normocytic anemia with polychromatophilia and numerous nucleated red blood cells. The white blood cells showed a marked leukemoid reaction, and the platelets also appeared to be markedly increased. The patient died very suddenly before further studies could be made.

Diagnosis at the time of surgery was giant follicular lymphoma of the spleen and of the nodes removed. Many patients have been comfortable for a number of years following removal of a single lymphoma. The immediate cause of death in this case was multiple thrombi in the pulmonary system and generalized retroperitoneal Hodgkin's disease. This case demonstrates the favorable effect of splenectomy in secondary hypersplenism but emphasizes that the course of the primary disease is not altered. The patient was able to work for 3 years postoperatively, and therefore, we believe the splenectomy was worth while.

Idiopathic Rupture of Congenital Aneurysm of the Splenic Artery

A white female, aged 29 years, para 3, gravida 2, who was 7 months pregnant, was admitted as an emergency. She was acutely ill with a temperature of 100.6, blood pressure 150/80, and pulse 136. The abdomen was moderately distended. The red blood cell count was 2,500,000; hemoglobin 5.5 grams; white blood cell count 13,900. The patient was operated upon for a possible ruptured uterus, and approximately 2,000 cubic centimeters of blood were found free in the peritoneal cavity. Exploration revealed a ruptured aneurysm of the splenic artery at the hilus, and a splenectomy was done. Seven hundred cubic centimeters of the blood in the peritoneal cavity was used in an autotransfusion. She had a rather stormy postoperative course but made a satisfactory recovery. The fifth postoperative day she gave birth to a premature infant which expired.

Congenital deformities of the spleen are rare. The aneurysms arise from defects in the formation of the vessels. The exact mechanism is not known. An idiopathic rupture during pregnancy was encountered and the successful surgical result obtained with splenectomy. Our patient did not have a splenic tumor which has been mentioned in the literature as being associated with a congenital aneurysm as reported by Cole. There was no history of trauma in this case to produce the rupture.

DISCUSSION

The pathologic picture of the spleen in hypersplenism generally is not diagnostic. The spleen is not palpably enlarged in essential idiopathic thrombocytopenic purpura. Splenomegaly is present in all other varieties, both primary and secondary. Microscopically, the spleen may have the characteristic appearance described by Leffler who has reported a prominent pale zone of medium and large lymphocytes surrounding the malpighian corpuscles. This appearance is illustrated in Figures 1 and 2.

In addition to routine laboratory procedures, pertinent diagnostic measures in hypersplenism are a sternal marrow aspiration, liver biopsy, and splenic aspiration. The bone marrow should preferably show hyperplasia of the normal elements. The study of the bone marrow may reveal the nature of the basic disease process in secondary hypersplenism.

A preoperative liver biopsy may be useful in recognizing cirrhosis of the liver, leukemic infiltration of the liver, and agnogenic myeloid metaplasia. A hemorrhagic tendency is a contraindication to preoperative liver biopsy. The technique, utilizing the Silverman needle, is not difficult. Local anesthesia will usually suffice, although in apprehensive patients a brief pentothal anesthesia may be necessary. A 6-hour period of observation for bleeding following the biopsy is recommended. We have had no complications following this procedure. A liver biopsy at the time of laparotomy should be routine. A preoperative splenic aspiration is found to be of value in an occasional difficult diagnostic problem, but it should not be a routine procedure. Emphasis should be made that the material ob-

tained from splenic aspiration is for cytologic examination only. Attempts to obtain tissue by a biopsy of the spleen may be dangerous. The technique of Ferris appears to be a safe method. Necessary precautions are as follows: There should be no bleeding tendencies, the patient should be conscious, and if the spleen is tender or painful, the procedure should not be attempted. The patient should be placed in the supine position. A 22 gauge spinal needle is passed between the ninth and tenth interspaces in the midaxillary line while the patient holds his breath. Again it should be emphasized that no attempt should be made to obtain a large amount of aspirate but only enough material to fill the spinal needle. A period of observation of at least 6 hours following the procedure is recommended. We have had no complications when this method was used. Presence of precursors of erythrocytes, leucocytes, and thrombocytes are suggestive of the diagnosis of extramedullary hematopoiesis when found in a splenic aspirate. Immature cells of only one element are suggestive evidence of conditions other than extramedullary hematopoiesis. Rarely, another abdominal tumor which has not been recognized by other diagnostic methods may be discovered. The lipoid storage diseases may be well demonstrated in cytologic examination of splenic aspirates.

The surgical treatment of primary hypersplenism is well standardized and consists of a properly timed splenectomy after adequate preparation. ACTH and cortisone are of value preoperatively in the hemolytic crisis and the hemorrhagic exacerbations. Elliott has described the uses of these steroids. Large doses are required, and the result is usually only of a temporary nature, but their employment may be lifesaving. The failure to produce a remission by use of adrenal steroids does not necessarily mean that splenectomy will be of no value. Moreover, steroids have been known to have a favorable effect when splenectomy has failed or in recurrence years after removal of the spleen. Early surgical intervention is proper in primary hypersplenism, and splenectomy during a remission results in a lower morbidity and mortality. The greater incidence of gallstones in hereditary spherocytosis as age advances is a factor in influencing us to recommend removal of the spleen at the age of 4 or 5 years. Removal of gallstones is not done at the time of splenectomy.

Of the splenectomies performed for hypersplenism, two-thirds are done for the primary type and one-third for the secondary type. Splenectomy for secondary hypersplenism should be undertaken only after considerable observation and with caution. The remissions are not clear-cut and the disease may be progressive. Speaking of splenectomy as a "cure" for hypersplenism probably is erroneous. Rather a "favorable result" is more nearly correct. Ninety per cent of the patients operated on for primary hypersplenism have a favorable result while only 50 per cent of those operated on for secondary hypersplenism will so benefit. The mortality of splenectomy for primary hypersplenism is 2 per cent and that for secondary hypersplenism is 15 per cent, and the ability to predict a good result following operation has not been attained completely at this time.

Splenectomy is most easily accomplished through a left upper abdominal transverse incision of sufficient size to remove the organ. A careful meticulous technique must be observed in order to avoid postoperative bleeding, and we believe individual ligation of the vessels is necessary. The splenic artery is ligated near the tail of the pancreas after the gastrocolic omentum has been divided. After the splenic artery has been figated, transfusions can be given without danger of producing a hemolytic crisis. The veins are then tied individually in the hilus of the spleen to avoid inclusion of the pancreas in the ligatures.

Postoperatively, the platelet count should be followed daily. A count of over 1,000,000 is an indication for the use of anticoagulants which may prevent a serious complication such as thrombosis of the portal vein.

The embryology of the spleen determines the location of accessory spleens which occur in 15 to 20 per cent. The spleen originates in the dorsomesogastrium. Therefore, accessory spleens are usually located in the splenic pedicle, the gastrocolic omentum, or the greater omentum, but they have been known to occur anywhere in the abdomen. They are small, may be multiple, may hypertrophy, and function after the primary spleen has been removed. Failure of splenectomy to affect a change in the course of the patient's disease may be attributed to an accessory spleen which has not been removed at the primary operation. Thorotrast studies may be of value in locating "missed" accessory

spleens, and operation should be attempted only after localization.

Contraindications to splenectomy are a hypoplastic bone marrow, acute splenic tumors, and such definitive diseases as malaria, subacute bacterial endocarditis, kala-azar, paroxysmal nocturnal hemoglobinuria, and Mediterranean and sickle cell anemia.

CONCLUSIONS

Primary hypersplenism is relatively easy to recognize, and splenectomy is the treatment of choice. A high percentage of favorable results may be expected. The diagnosis of secondary hypersplenism may be difficult, and aids in recognizing this syndrome are discussed. Here, good results of splenectomy are less constant and more difficult to predict. Improvement in the symptom complex of secondary hypersplenism following splenectomy has been observed, but the course of primary disease is not altered. A case of essential idiopathic thrombocytopenic purpura and one of idiopathic rupture of a congenital splenic arterial aneurysm, both occurring during pregnancy, are presented. A prominent pale zone of medium and large lymphocytes surrounding the malpighian corpuscle in hypersplenism is confirmed.

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5. McElin, T. W., Mussey, R. D., and Watkins, C. H. Splenectomy during pregnancy. Am. J. Obst. Gyn., 1950, 59: 1036.

THE SURGEON'S LIBRARY

Reviews of New Books

THE AUTHOR of the monograph on the painful heel, *Der Fersenschmerz*,[1] is professor and chief surgeon at the Wurzburg University Clinic. He considers the heel as a barometer for the state of the foot. All of the organic and functional disturbances which occur in the region of the heel and the Achilles tendon are included in the study of the painful heel. This is a difficult and complicated task since the painful heel can be the expression of functional decompensation, poor posture, or a local weakness. In addition one has to consider all inflammatory processes such as arthritis in all its various forms and the specific diseases that involve the bone as well as growth disturbances such as occur in the apophysis.

The author bases his subject matter on his own experience as well as a review of the literature. An analysis and description of all the possibilities that can cause a painful heel aids the practicing physician in diagnosis. To understand the etiologic factors is in itself a help in treatment. In many instances the painful heel is due to foot strain.

The author describes the diseases of the Achilles tendon and the tendon sheath. He describes the various types of bursitis and periosteal inflammation including calcaneal spurs and apophyseal changes in the back of the heel. For conservative treatment he uses arch supports. He describes the various types of surgery including the subcutaneous division of the plantar fascia for relief of the calcaneal spur. Tuberculosis and osteomyelitis are considered and ulcers of the heel and fractures of the os calcis are included. Finally, there is a chapter on the soft tissue and bone tumors which occur in this area. He emphasizes the importance of the recognition and treatment of the many disorders of the heel that occur as the result of chronic strain or functional decompensation.

The monograph is well illustrated with excellent reproductions of photographs and roentgenograms as well as line drawings. —*Emil D. W. Hauser.*

THE AUTHOR, George Schaefer, with his extensive experience and broad reading has compiled into book form a vast amount of up-to-date information in *Tuberculosis in Obstetrics and Gynecology*.[2] It is presented in such a manner that the obstetrician and gynecologist can understand the general aspects of tuberculosis and also the specific details as applied to our specialty. It provides an excellent summary of available information from which the general practitioner and the specialist can quickly obtain guidance. This book fills a much needed gap and should be useful to everyone who is interested in this disease or who occasionally encounters an obstetric or gynecologic patient with tuberculosis. The latter is not so infrequent since at least 32,000 pregnant women with known tuberculosis are delivered in the United States annually. Enthusiastic recommendation of this book is quite in order. —*John I. Brewer.*

THE BOOK, *Surgery of the Eye—Diseases*[3] by Alston Callahan, is a superb companion piece to his earlier test on the surgery of ocular trauma, and, since it is more comprehensive, it is of even greater value than the preceding volume to the average ophthalmic surgeon. It presents the same imaginative verbal and pictorial detail and with these two volumes and Duke-Elder's seven, the English speaking ophthalmologist is now prepared for any eventuality.

After an introductory chapter on anesthesia and other operative details, surgical diseases of the eye are considered in an anterior-posterior direction. Perhaps the most valuable portion of each chapter is that devoted to indications for surgery and to the various operative procedures available for a given surgical situation. However, in contrast with many other surgical texts (both foreign and American) the author indicates specifically which he believes is the procedure of choice. The exhaustiveness of the discussion is best illustrated by the section on glaucoma to which the author devotes 5 full chapters.

Another noteworthy chapter is that on orbital implants. Callahan has personally evaluated almost all of the various types available, and since he has not devised one himself, his advice is reliable. This may be said of all of Callahan's sober and thoughtful book (in spite of the advocation of autohemotherapy for postoperative and traumatic hyphema).

This is a handsome book of large size and, as has come to be expected of the author, the illustrative material is magnificent. This is particularly true of the three-dimensional drawings that profusely illustrate

[1] DER FERSENSCHMERZ; FUNKTIONELLE UND ORGANISCHE STOERUNGEN IM BEREICH DER FERSE UND ACHILLESSEHNE. By Prof. Dr. K. Stucke. 163 pages, 68 illustrations. DM 29.70. Stuttgart: Georg Thieme Verlag, 1956.

[2] TUBERCULOSIS IN OBSTETRICS AND GYNECOLOGY. By George Schaefer, M.D., F.A.C.S., F.I.C.S. 307 pages, 54 illustrations. $8.75. Boston and Toronto: Little, Brown & Co.

[3] SURGERY OF THE EYE—DISEASES. By Alston Callahan, M.D., F.A.C.S. 447 pages, 263 illustrations. $25.00. Springfield, Ill.: Charles C Thomas, 1956.

the various surgical procedures. Unfortunately, the illustrator is not named in the introduction, but most of the drawings are signed by an A.B. Arthur, to whom much credit must go for the handsome appearance and value of this book. *In toto* this text is a masterful accomplishment and should be in the library of every ophthalmologist, be he a novice or an accomplished ophthalmic surgeon. —*David Shoch.*

THE VOLUME ENTITLED *Der Herzkatheterismus bei angeborenen und erworbenen Herzfehlern*,[4] intended by the authors to fill a gap remaining in the German literature, gives a clear description of the instrumentation, techniques, and complications of cardiac catheterization as carried out in their laboratory. Most of the book is devoted to a special section in which the physiologic data obtainable by cardiac catheterization in the various forms of congenital and acquired heart disease are discussed. The physiologic interpretations of their findings, in general, agree with those in this country. A notable exception is found in the explanation of arterial blood oxygen desaturation in cases of congenital heart disease associated with pulmonary hypertension in which the authors incriminate a defect in pulmonary diffusion in addition to an existent right-to-left shunt. Since this book was written some time ago, the newer techniques employing selective angiocardiography, indicator dilution curves, and immediate reading oximeters now considered essential in diagnostic cardiac catheterization are not described. A good bibliography is appended and the book should serve as a useful introduction to this subject. —*I. J. Fox.*

IN THE EDITOR'S PREFACE of *Forceps Deliveries*,[5] it is stated "The delivery of a living child by forceps is still the most frequent and important major operation in obstetrics." The author's awareness of this dictum is the essence of his presentation in this clear, concise, and well written book on forcep deliveries.

Dennen stresses that there is no one kind of forceps adaptable to all cases and he emphasizes the importance of knowing the limitations of various types of forceps. The choice of forceps should be influenced by the type of pelvis, the mechanism of labor, and the position of the presenting part.

The introduction by the author contains many practical and valuable rules in the good conduct of forcep deliveries which indicate his sound teachings.

He states that the object of this book is to present his opinion that "one should use the type of forceps that suits the individual case rather than make all cases fit one type of forceps."

Dennen's classification of forcep deliveries differs from the standard types in most textbooks. He states that the long distance from low to midpelvis and the short distance from mid to high pelvis have led to numerous errors in classification. He is of the opinion that this classification should be based on the relationship of the biparietal diameter of the head to the four planes of the pelvis rather than a division into high, median, and low types.

The author's presentation of the use of the Kielland, Barton, and Pifer forceps is especially well presented. The chapter on prerequisites and technique of forcep application with the exceptionally clear and detailed illustrations, which constitutes one of the more attractive features of this excellent presentation, make this book invaluable to all physicians who teach and practice the art of obstetrics. —*Magnus P. Urnes.*

THE SECOND EDITION of the *Handbuch der gesamten Unfallheilkunde*[6] is published in 3 volumes. It lists 51 contributing authors, and is a comprehensive collection of information concerning compensable illness: accidental injury, occupational and industrial injury and disease, occupational aggravation of pre-existing disease, and the like. Perhaps the best English translation of the title would be *Handbook of Compensation Medicine*. This review concerns only Volumes I and II.

Volume I is organized into 4 sections. The first 2 of these are devoted to historical, legal, and general aspects of private and public compensation for illness. Psychologic and environmental factors, prevention, simulated injuries, self-inflicted injuries, and medical opinions as they affect compensation, are discussed. There is in these sections an emphasis on failure of the individual. Psychic causes and effects are stressed. The third section encompasses accidental injuries: mechanical, thermal, electric, and radiation injuries. Wounds and wound infections, vascular injuries, injuries to nerves, muscles, tendons, bones, and joints are covered thoroughly and in detail. In the fourth and final section of Volume I compensation for medical diseases is discussed. This section includes infectious diseases, rheumatoid arthritis, blood dyscrasias, neurologic diseases, and psychiatric manifestations.

Each injury or disease is presented with its legal aspects. The discussion of each entity relates to the formation of an opinion concerning compensability. The thoroughness with which ramifications are pursued may best be illustrated: for example, the subsection concerning nontraumatic neurologic diseases of the cord includes discussions of compensability in acute myelitis in its various forms, in multiple sclerosis, poliomyelitis, tabes dorsalis, spinal arachnoiditis, vascular disturbances, lathyrism, syringomyelia, degenerative diseases of the cord, and in the myopathies. Each entity is presented with sufficient general information, including pathophysiology, to enable the reader to follow the text without consulting other sources. Definitions of damage and its causes are precise, and discussions of the basic aspects of trauma are detailed. Sequelae and complications are stressed. One is left with the distinct impression, and perhaps a feeling of envy, that there is a bit more responsibility in Germany on the part of the patient to prove the relationship of his disability, if any, to an injury. Exceptions to this feeling are not infrequent.

[4]DER HERZKATHETERISMUS BEI ANGEBORENEN UND ERWORBENEN HERZFEHLERN. By Prof. Dr. O. Bayer, Dr. Fr. Loogen, and Dr. H. H. Wolter. With a foreword by Prof. Dr. E. Boden. 191 pages, 131 illustrations. $8.60. Stuttgart: Georg Thieme Verlag, 1954.

[5]FORCEPS DELIVERIES. By Edward H. Dennen, M.D., F.A.C.S. 228 pages, 91 illustrations. Philadelphia: F. A. Davis Co., 1955.

[6]HANDBUCH DER GESAMTEN UNFALLHEILKUNDE. Edited by Prof. Dr. H. Bürkle de la Camp, and Prof. Dr. P. Rostock. 2nd rev. ed., vols. I and II of a 3 volume set. Vol. I, 539 pages, 82 illustrations. DM 84. Vol. II, 590 pages, 106 illustrations. DM 89. Stuttgart: Ferdinand Enke Verlag, 1955.

The first 70 pages of Volume II are devoted to a thoughtful consideration of neoplastic diseases and their relationship to the problem at hand. Not all the opinions expressed in this section are accepted universally, but that is no criticism. In this section as elsewhere in these volumes, the attention given to detail is remarkable: for instance, the discussion of the effect of trauma in the development of metastatic neoplastic lesions, and of the compensable effect of trauma in delaying the diagnosis of malignant disease. Excellent examples are given. In general, the authors extend somewhat more credence to the role of trauma in the etiology of neoplastic processes than do many physicians in the United States. In the remainder of Volume II compensable illness is discussed in sections divided on a regional anatomic basis. These include the head, the chest cage and thoracic organs, the abdomen and abdominal organs, the genitourinary systems, and the spine and spinal cord.

A few tables of percentage of disability are included. Omissions are minor, and any criticism may be picayune. The discussion of caisson disease does not mention the effects of altitude. The adrenal glands seem slighted in the chapter on metabolic disease. Several chapters on bone and joint disease could have been tied more closely to the pertinent theme of the book. As they stand, these chapters are often indistinguishable from similar sections in works devoted to general orthopedics.

In both volumes illustrative case reports are used liberally, adding both information and interest. Experimental work is frequently cited where it is pertinent. Each chapter is followed by a bibliography, usually extensive and recent. References are also made in the text to additional source material. The various chapters, being the work of different authors, are informative and interesting in different degree. The chapters on injury due to electricity, those devoted to neurologic damage and to peripheral vascular injury, including thrombosis and embolism, are especially good. There is more than an occasional rare bit of information, such as that persons with renal damage are prone to die of ordinarily sublethal electric shocks.

The index at the back of each of these two volumes is brief. The reviewer hopes that the very large wealth of information, both specific and general, which these books contain, will be made more readily available by a complete cross reference index in Volume III.

These books contain much of interest to all physicians whose practice includes the evaluation of injury and its sequelae for purposes of compensation. They have special value as reference material for those engaged in insurance, industrial, occupational, and preventive medicine, and belong especially in libraries emphasizing these areas. They are clearly written, without undue dogmatism, and are excellently printed and bound. —*Elmer V. Dahl.*

VOLUME VI OF THE SERIES *Clinical Orthopaedics*,[7] edited by Anthony F. DePalma, is divided into two parts. The first half of the volume is devoted to a symposium on intramedullary prostheses for the hip joint. A group of well qualified authorities discuss indications and contraindications for the use of various prosthetic devices. In addition, articles include the choice of materials, the surgical approach for insertion of prostheses, and surgical technique. The discussion is a timely one as an attempt is made to re-evaluate the role of hip replacement prostheses in orthopedic surgery.

The second half of the book is a collection of individual papers. These include: "Detection of Chordoma," "Internal and External Fixation of Tibial Fractures," and "Management of Suppurative Arthritis Complicating Artificial Hips." Several case reports are also included in this section of the book.

The chief value of this volume lies in the first section, and will appeal particularly to orthopedic surgeons. —*William A. Larmon.*

ADVANCES IN THE THERAPY of cardiovascular disease in recent years, particularly those of a surgical nature, have greatly increased the necessity for early and accurate diagnosis in this field. At the same time development of specialized laboratory techniques, such as the cardiac catheter, has permitted more direct scrutiny of many of the traditional concepts of cardiovascular physiology than hitherto possible. The textbook entitled *Cardiac Diagnosis; a Physiologic Approach*,[8] presents up-to-date sampling of the basic principles governing the function of the heart in normal and abnormal conditions. These have been selected by the author to explain the mechanisms by which the various signs and symptoms of clinical cardiology are derived.

The book is divided into 5 sections, the first 3 of which are devoted to the aforementioned physiologic principles. In the fourth section current diagnostic methods are discussed from the standpoint of the physical principles involved. Emphasis is given to the limitations of the various laboratory techniques which, if not considered, may result in errors of interpretation. In the final section several specific categories of cardiac disease are considered to illustrate the practical utilization of physiologic concepts in making a clinical diagnosis.

The book is clearly written and is profusely illustrated with schematic drawings which are effectively employed in conveying the sense of a given idea to the reader. A proportion of the material deals with work carried out in the author's own laboratory. The author states that the book is intended for medical students and physicians at all stages of development. It is my opinion, however, that the readers who will achieve the greatest benefit from it are likely to be those with clinical experience seeking to "brush up" on current physiologic concepts and methodology. To these, the first 4 sections of the book will hold greater interest than the final one.

—*Gerry A. Smyth.*

TWENTY-SIX EXCELLENT PAPERS, contributed by an impressive group of distinguished authors, comprise the second series of *Modern Trends in Obstetrics and*

[7]CLINICAL ORTHOPAEDICS. Anthony F. DePalma, Editor-in-Chief. With the Assistance of the Associate Editors, the Board of Advisory Editors, and the Board of Corresponding Editors. Number 6. 219 pages, illustrated. $7.50. Philadelphia and Montreal: J. B. Lippincott Co., 1955.

[8]CARDIAC DIAGNOSIS; A PHYSIOLOGIC APPROACH. By Robert F. Rushmer, M.D. 447 pages, illustrated. $11.50. Philadelphia and London: W. B. Saunders Co., 1955.

Gynaecology[9] edited by Kenneth Bowes. The subjects have been chosen so that they encompass most of the recent fields of interest in both clinical and investigative obstetrics and gynecology.

Throughout the book there has been adherence to the principle that a contributor whose name is linked with and who knows a great deal about his subject should present it. A few examples, among the many, of how this principle has been used include the chapters on "The Ovarian Vasculature and Ovarian Functions" by S. R. M. Reynolds, "The Cellular Components of the Human Ovary" by J. D. Boyd and W. J. Hamilton, "The Mechanism of Myometrial Function and Its Disorders" by Arpad Csapo, "The Sex Chromatin and Its Application to Errors in Sex Development" by M. L. Barr, "The Forceps Operation in Modern Obstetrics" by T. N. A. Jeffcoate, "The Early Diagnosis of Intersex" by D. Innes Williams, and "Antibiotics in the Treatment of Genital Tuberculosis in the Female" by Ake B. V. Rydén.

A number of chapters, written by specialists in basic sciences, reveal certain trends in research on fundamental problems in obstetrics and gynecology. Other chapters, written by clinical investigators and teachers, summarize lines of progress in clinical matters. More chapters deal with the research than they do with the clinical aspects of the specialty and more emphasis is placed on gynecologic than on obstetric problems.

The book also presents numerous excellent examples of research applied to clinical medicine. There is something worthwhile in it for anyone interested in obstetrics and gynecology. It should be particularly appealing to those who wish to, but do not have the facilities for keeping up with recent trends and it ought to be a valuable reference for men studying for their Board examinations. —*John W. Huffman.*

THE MONOGRAPH ENTITLED *Body Fluids in Surgery*[10] by A. W. Wilkinson is an excellent, penetrating book on this subject.

In order to understand a given situation it is first necessary carefully to examine the causes which have produced the situation. It is with such a viewpoint that the author deals with this subject. The intention of the author is to provide in a convenient form, first, a sufficient basic understanding of the behavior of body fluids in health and disease, and, second, to provide for management of disturbances of the body fluids as they occur in surgical patients. He has succeeded in both.

The discussion of potassium and the less well understood role of magnesium are of particular interest. The general principles in the treatment of fluid disturbances are: (1) to insure survival by maintaining and adequate volume of blood in active circulation; (2) to stop the loss of fluid; and (3) to repair the damaged and distorted body fluid pattern by the administration of an appropriate combination of water and electrolyte.

The methods of treatment presented are sound and well planned. This book can be enthusiastically recommended to every surgeon.

—*Russell T. Bothe.*

THE VOLUME ENTITLED *Die Fruehdiagnose des Uteruscarcinoms*[11] is devoted to the early diagnosis of uterine carcinoma. Because of the worldwide interest in carcinoma in situ of the cervix, the author has changed his book considerably in this third edition. He himself has now had experience with 20,000 carcinoma smears. He includes chapters on the histologic diagnosis of carcinoma in situ, beginning invasion, colpophotography, cancer in situ, and pregnancy and statistics about cancer of the cervix. Considerable data are included about treatment of carcinoma in situ. There is also a section dealing with aerobic and anaerobic glycolysis and respiration of benign and malignant epithelial proliferations.

As is well known there is no unity of opinion concerning carcinoma in situ found during pregnancy. Limburg is of the opinion that cancer in situ discovered in a pregnant woman generally persists as such and should be considered in the same light as carcinoma in situ in a nongravid woman. Limburg points out that timely treatment of carcinoma in situ will reduce the incidence of invasive carcinoma of the cervix and, furthermore, improve the results of therapy.

The book is well written and abundantly illustrated. Some illustrations are in beautiful colors. All the authorities, especially the American ones, on the subject of carcinoma of the cervix are quoted. At the end of the book is a comprehensive list of the papers and books devoted to this subject. The author has written an excellent book which will certainly be helpful to German reading physicians.

J. P. Greenhill.

DOCTOR STIMSON HAS AGAIN REVISED the very handy little book entitled *A Manual of Fractures and Dislocations.*[12]

This book is particularly useful to interns and residents and general practitioners as a ready reference for common fractures of the extremities and spine. It covers most of the common fractures and is written in simple, direct language. The illustrations are all line drawings which are simplified and depict the usual displacements that occur with fractures and the methods of reduction and immobilization commonly used. The book is useful in that it is brief and to the point and tends to treat fractures on a sound conservative basis but makes recommendations for open reduction when it is warranted.

—*William A. Larmon.*

[9] MODERN TRENDS IN OBSTETRICS AND GYNAECOLOGY. (Second Series). Edited by Kenneth Bowes, M.D., M.S. (Lond.), M.B., Ch.B. (L'pool), F.R.C.S., F.R.C.O.G. 407 pages, 176 illustrations. $12.00. New York and London: Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., 1955.

[10] BODY FLUIDS IN SURGERY. By A. W. Wilkinson, Ch.M., F.R.C.S.E. 212 pages, 6 illustrations. $4.00. Baltimore: The Williams & Wilkins Co.; Edinburgh and London: E. & S. Livingstone Ltd., 1955.

[11] DIE FRUEHDIAGNOSE DES UTERUSCARCINOMS; HISTOLOGIE, KOLPOSKOPIE, KOLPOPHOTOGRAPHIE, CYTOLOGIE, BIOCHEMISCHE METHODEN. By Prof. Dr. Med. Hans Limburg. 334 pages, 122 illustrations. 3rd enl. rev. ed. DM 36.—$8.60. Stuttgart: Georg Thieme Verlag, 1956.

[12] A MANUAL OF FRACTURES AND DISLOCATIONS. By Barbara Bartlett Stimson, A.B., M.D., Med.Sc.D., F.A.C.S. 3rd ed., thoroughly rev. 224 pages, 97 illustrations. $4.50. Philadelphia: Lea & Febiger, 1956.

THE FOURTH EDITION of *Modern Operative Surgery*[13] is being published in 2 volumes, the first volume now being available and here reviewed. This edition of the text was being prepared and edited by the late G. Grey Turner at the time of his death. He had previously edited Volumes II and III. Volume IV was completed under the editorship of Lambert Charles Rogers. The foreword to the book is by Sir Gordon Gordon-Taylor, and the work is dedicated to its deceased senior author, G. Grey Turner.

Volume I has been written by 38 contributors, and the material presented represents, for the most part, surgical thinking and practice in Britain. This volume includes the fields of orthopedic, thoracic, cardiac and great vessel, spinal cord, and nerve surgery. A good chapter on "Principles of the Operative Treatment of Malignant Disease" is included. Following this are chapters on the breast, abdominal injuries, the gastrointestinal tract, the liver, the pancreas, and the spleen.

Emphasis is placed on the use of correct surgical judgment. The technical aspects of operations are partially covered. Nomenclature and terminology vary a little from that occurring in the American literature. Certain medicinals, antiseptics, and antibiotics commonly in use in the United States during the past 5 to 10 years are not included. Statistics included in portions of the text, on the breast in particular, should be brought up to date. Cardiac surgery has progressed very rapidly, and this section is complete except for the recent advances in open heart surgery.

Regardless of the foregoing minor criticisms, the book is interestingly written, contains a wealth of information on the subjects covered, and would be of value to any student of surgery. Illustrations are mainly diagrammatic and easily understood. The volume is well indexed. —*Oliver H. Beahrs.*

[13]MODERN OPERATIVE SURGERY. Edited by the late G. Grey Turner, LL.D., D.Ch., M.S., F.R.C.S., F.R.A.C.S., F.A.C.S., and Lambert Charles Rogers, V.R.D., M.Sc., M.D., F.R.C.S., F.R.C.S.E., F.R.A.C.S., F.A.C.S. With a foreword by Sir Gordon-Taylor. 4th ed., in two volumes. Vol. I. 1229 pages, 476 illustrations. $15.00. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., 1956.

IT IS EXACTLY 2 YEARS AGO that my review of Martius' third edition of *Lehrbuch der Gynaekologie* appeared in these pages. The fourth edition[14] contains exactly the same number of pages and illustrations as the third. The changes made in this edition concern the following: neurohormonal regulation and its disturbances, irregularities of menstruation, pelvic tuberculosis, genital abnormalities, and the Meigs syndrome. Of interest is Martius' attitude about carcinoma in situ. He calls this condition surface carcinoma (Oberflächenkarzinom) and maintains that it has not been proved that this is or is not a true carcinoma. For this reason he designates this entity as so-called surface carcinoma.

In general the book has the contents and appearance of the previous editions. It is an excellent textbook of gynecology and it will undoubtedly continue to maintain its prominent position among all books on this subject. I congratulate Martius again.

J. P. Greenhill.

[14]LEHRBUCH DER GYNAEKOLOGIE. By Prof. Dr. Med. Heinrich Martius. With the collaboration of Kathe Droysen. 4th rev. ed. 414 pages, 446 illustrations. DM 49.80. Stuttgart: Georg Thieme Verlag, 1956.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

OBSERVATIONS ON KREBIOZEN IN THE MANAGEMENT OF CANCER. By A. C. Ivy, Ph.D., M.D., John F. Pick, S.B., M.D., and W. F. P. Phillips, M.D. 107 pages, 5 illustrations. $2.50. Chicago: Henry Pegnery Co., 1956.

SIR WILLIAM ARBUTHNOT LANE, BT; AN ENQUIRY INTO THE MIND AND INFLUENCE OF A SURGEON. By T. B. Layton, D.S.P., M.S. 128 pages, 8 illustrations. $4.75. Baltimore: The Williams & Wilkins Co.; Edinburgh and London: E. & S. Livingstone Ltd., 1956.

NOUVELLE PRATIQUE CHIRURGICALE ILLUSTRÉE. By Jean Quénu. Fascicule 9. 265 pages, 227 illustrations. 2.500fr. Paris: G. Doin & Co., 1956.

DERMATOLOGY. By Donald M. Pillsbury, M.D., Walter B. Shelley, M.D., and Albert M. Klingman, M.D. 1331 pages, 564 illustrations. $20.00. Philadelphia and London: W. B. Saunders Co., 1956.

ROENTGEN SIGNS IN CLINICAL DIAGNOSIS. By Isadore Meschan, M.A., M.D. With the assistance of R. M. F. Farrer-Meschan, M.B., B.S. 1058 pages, 2216 illustrations on 780 figures. $20.00. Philadelphia and London: W. B. Saunders Co., 1956.

AN ATLAS OF ANATOMY. By J. C. Boileau Grant, M.C., M.B., Ch.B., F.R.C.S.(Edin.). 4th ed. 634 pages, 8 illustrations. $15.00. Baltimore: The Williams & Wilkins Co., 1956.

TEXTBOOK OF GYNECOLOGY. By Emil Novak, M.D., F.A.C.S., and Edmund R. Novak, M.D., F.A.C.S. 5th ed. 840 pages, 543 illustrations. $11.00. Baltimore: The Williams & Wilkins Co., 1956.

COMYNS BERKELEY'S PICTORIAL MIDWIFERY; AN ATLAS OF MIDWIFERY FOR PUPIL MIDWIVES. Revised by D. M. Stern, M.A., M.B., Ch.B. (Cantab.), F.R.C.S., F.R.C.O.G. 5th ed. 164 pages, 224 illustrations. $3.75. Baltimore: The Williams & Wilkins Co., 1956.

WILLIAMS OBSTETRICS. By Nicholson J. Eastman, M.D., Ph.D. 11th ed. 1212 pages, illustrated. New York: Appleton-Century-Crofts, Inc., 1956.

HUMAN GENERATION; CONCLUSIONS OF BURDACH, DÖLLINGER AND VON BAER. By Arthur W. Meyer. 143 pages, 9 illustrations. $3.50. Stanford, California: Stanford University Press, 1956.

THE PATHOLOGY AND SURGERY OF THE VEINS OF THE LOWER LIMB. By Harold Dodd, Ch.M.(L'pool),

F.R.C.S.(Eng.), and Frank B. Cockett, M.S.(Lond.), F.R.C.S.(Eng.). 462 pages, 313 illustrations. $12.50. Baltimore: The Williams & Wilkins Co., 1956.

THE INITIAL MANAGEMENT OF THORACIC AND THORACO-ABDOMINAL TRAUMA. By Lawrence M. Shefts, M.D. 121 pages, illustrated. Springfield, Illinois: Charles C Thomas, 1956.

ETIOLOGIC FACTORS IN RENAL LITHIASIS. By Arthur J. Butt, B.S., M.D., F.A.C.S. 401 pages, illustrated. $12.50. Springfield, Illinois: Charles C Thomas, 1956.

PELVIMETRY. By Herbert Thoms, M.D. 120 pages, 45 illustrations. $5.00. New York: Paul B. Hoeber, Inc., 1956.

MEDICAL ASPECTS OF TRAFFIC ACCIDENTS. By Harold Elliott, M.D., editor. 511 pages, illustrated. $7.00. Montreal, Canada: Sun Life Insurance Co. of Canada, 1956.

POTT'S PARAPLEGIA. Edited by D. Ll. Griffiths, H. J. Seddon, and R. Roaf. 129 pages, 30 plates. London, New York, and Toronto: Oxford University Press, 1956.

CARE OF THE LONG-TERM PATIENT. Pubished for the Commonwealth Fund's Commission on Chronic Illness. Vol. II. 606 pages, not illustrated. $8.50. Cambridge, Mass.: Harvard University Press, 1956.

UROLOGY AND INDUSTRY. By Leonard Paul Wershub, M.D., F.A.C.S. 151 pages, not illustrated. $5.00. Springfield, Illinois: Charles C. Thomas, 1956.

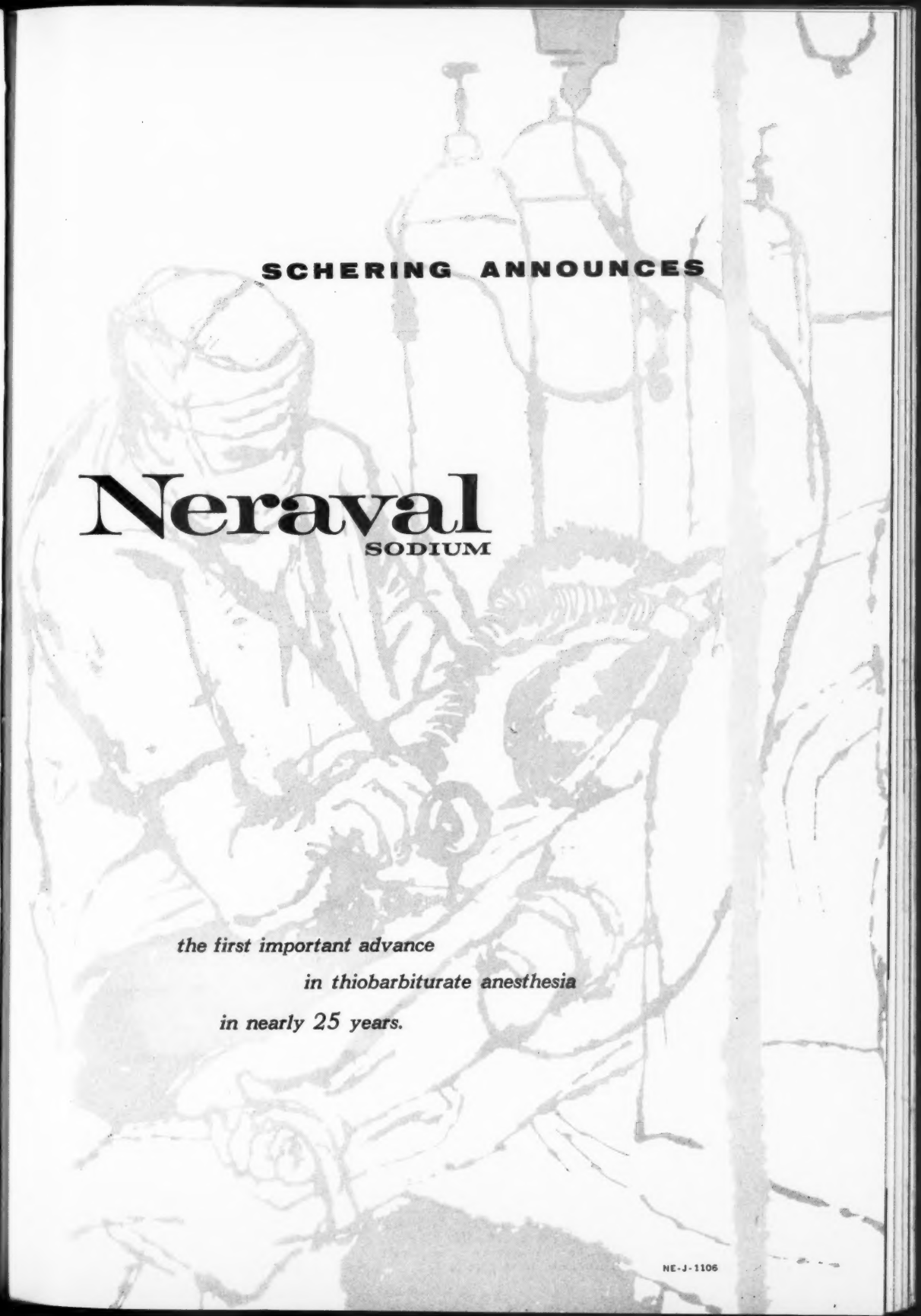
ORGANIZED HOME MEDICAL CARE IN NEW YORK CITY; A STUDY OF NINETEEN PROGRAMS. By the Hospital Council of Greater New York. 538 pages, not illustrated. $8.00. Published for the Commonwealth Fund. Cambridge, Massachusetts: Harvard University Press, 1956.

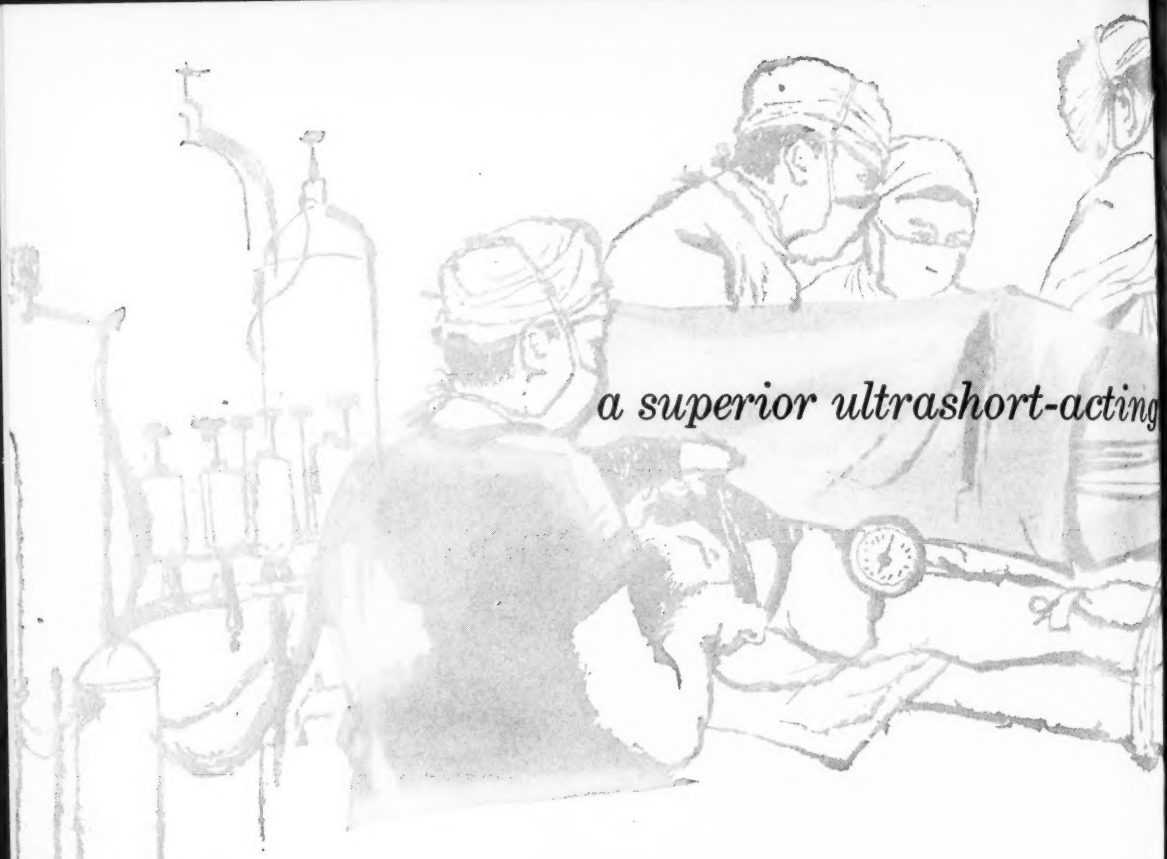
GYNÄKOLOGIE IN DER TAGLICHEN PRAXIS. By Dr. med. habil. Walter Stemmer. 200 pages, 16 illustrations, and 1 table. Ganzleinen DM 19.80. Stuttgart: Hippokrates-Verlag GMBH, 1956.

Correspondence

THE INADEQUACY OF SURVIVAL RATES IN THE EVALUATION OF CANCER THERAPY—*A Correction.*

DR. CHANDLER SMITH, the author of the article entitled "The Inadequacy of Survival Rates in the Evaluation of Cancer Therapy" which appeared in the September issue, wishes to make a correction in a statement which he made on page 311. This sentence reading: "The amount of tissue cleared of tumor is an infallible guide to the superior method of treatment" should read: "The amount of tissue cleared of tumor is an infallible guide to the superior therapeutic accomplishment."


SCHERING ANNOUNCES
Neraval
SODIUM
the first important advance
in thiobarbiturate anesthesia
in nearly 25 years.
NE-J-1106



a superior ultrashort-acting intr

"...THE SHORTEST-ACTING THIOBARBITURATE SO FAR KNOWN TO US..."[1]

Prolonged depression in both long and short-term procedures imposed many limitations on the use of earlier thiobarbiturates. NERAVAL, with its extremely rapid detoxification, considerably reduces these restrictions and opens up many new areas for the use of barbiturate anesthesia.

In addition, NERAVAL – by shortening the period of postoperative incapacity and depression – makes the procedure safer, more pleasant for the patient.

Lower milligram potency and more rapid detoxification of NERAVAL compared with thiopental and thiamylal provide greater clinical safety and better moment-to-moment control. NOTE: for equivalent anesthetic effect approximately 1½ to 2 times as much NERAVAL is usually required.

PACKAGING:

NERAVAL Sodium Sterile Powder: vials of 1 and 2 Gm., boxes of 6 and 25; vials of 5 Gm., boxes of 1 and 25.

BIBLIOGRAPHY:

1. Boone, J.D.; Munoz, R., and Dillon, J.B.: Anesthesiology *17*:284, 1956. 2. Zima, O.; von Werder, F., and Hotovy, R.: Anaesthesist *3*:244, 1954. 3. Fitzpatrick, L.J.; Clarie, D'A., and Mersch, M.A.; To be published. 4. Blake, M.W. and Perlman, P.L.: J. Pharmacol. & Exper. Therap. *117*:287, 1956. 5. Ayd, F.J., Jr.: Neraval: A new anesthetic for electroconvulsive therapy, paper presented at annual meeting, Electroshock Research Association, Chicago, Illinois, April 29th, 1956. 6. Irwin S.; Stagg, R.D.; Dunbar, E., and Govier, W.M.: J. Pharmacol. & Exper. Therap. *116*:317, 1956. 7. Reifferscheid, M., and Dietmann, K.: Deutsche med. Wchnschr. *79*:638, 1954. 8. Dietmann, K.: Deutsche med. Wchnschr. *79*:1748, 1954.

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YOU CAN CONFIRM THESE CLINICAL EXPERIENCES WITH NERAVAL

- Significantly faster detoxification and elimination than either thiopental or thiamylal. [1,2]
- Shorter duration of action.[1]
- Considerably less accumulation.[3,4,6]
- More rapid, complete recovery.[3,5-7]
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1 EXCLUSIVE *DISPENSO-REEL*

Suture spins off easily without kinking. Pre-cut lengths are ready for instant use in one continuous motion—no back-and-forth unwinding or untangling of loose coils.

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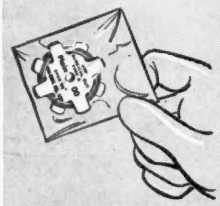
TWIN *Dispenso-reel* protects needle against dulling—needle cannot cut against suture or puncture the packet.



3 STERILE PLASTIC PACKET

Needled sterile suture instantly available without danger and mess of broken glass. Label is easy to read. Convenient, time-saving single plastic packet is leakproof and unbreakable.

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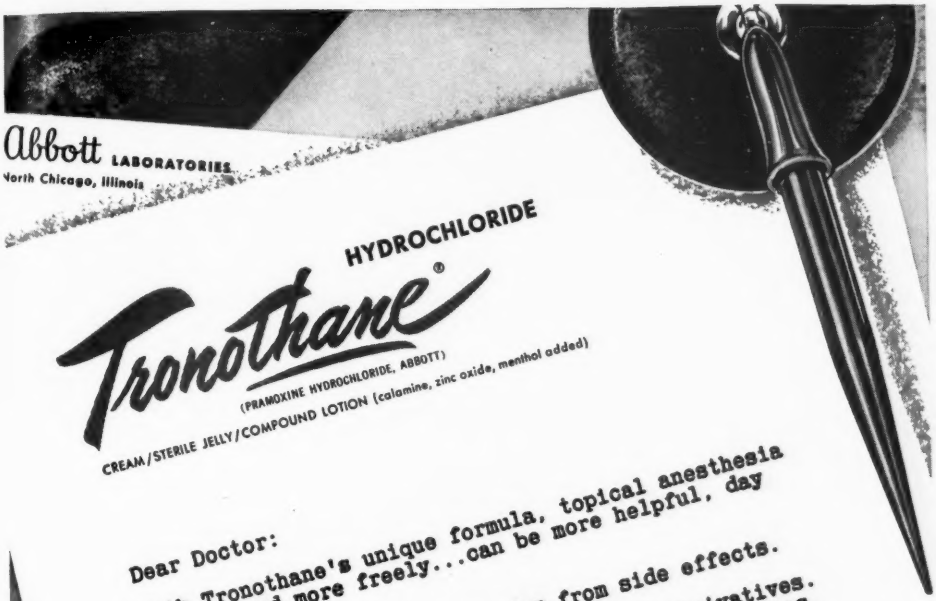

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A goodly portion of the minerals in the oat seed is concentrated in the embryo and the outer cellular layers. Since only the inedible hulls are removed in the milling process, the entire mineral content of the edible whole grain is retained in ready-to-cook oatmeal.

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1. Watt, B.K., and Merrill, A.L.: Composition of Foods—Raw, Processed, Prepared—Washington, D.C., United States Department of Agriculture, Agricultural Handbook No. 8, 1950.

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In the aim for optimal nutrition without undue weight gain during the entire prenatal period, oatmeal serves well as a universally accepted food high in nutrient value without "empty" calories.

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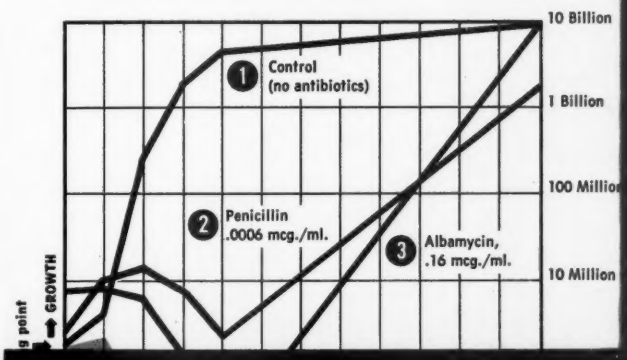
This graph shows the growth rate of a penicillin- sensitive strain of Staphylococcus (Micrococcus pyogenes, var. aureus) under 3 conditions:

1. In the absence of antibiotics
2. In the presence of subinhibitory concentration of penicillin
3. In the presence of subinhibitory concentration of Albamycin*



Now lift this transparency and see what happens when **half these amounts of penicillin** and Albamycin are **combined!**

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*Trademark, Reg. U.S. Pat. Off.—The Upjohn brand of crystalline novobiocin sodium.
Data: Upjohn Research Laboratories (3265—ARB—119)

average dosage only t.i.d.

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Alba-Penicillin*

(Albamycin plus penicillin)

Compare it with th ibiotic you are currently using:

Range of effectiveness: Alba-Penicillin is effective against the organisms that cause the overwhelming majority of bacterial infections (Staphylococci, Streptococci, Pneumococci, Proteus).

Risk of esistance: Because in vitro tests show this combination is synergistic against even Staphylococci **already** resistant to all other antibiotics, the risk of resistance is minimized.

Risk of enterocolitis: Because it has little or no effect on the predominant Gram-negative intestinal bacteria, and is highly effective against Staphylococci, there is virtually no danger of enterocolitis due to alteration in intestinal flora, or of other side effects such as perianal pruritus.

Convenience: Alba-Penicillin is oral therapy, and the average adult dosage is only **1 to 2 capsules t.i.d.**, which eliminates middle-of-the-night medication.

It is available in bottles of 16 capsules. Each capsule contains 250 mg. Albamycin (as novobiocin sodium, crystalline) and 250,000 units penicillin G potassium.

Upjohn

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There is less danger of infection following bowel surgery when SULFASUXIDINE is used before and after operation. Minimal absorption of SULFASUXIDINE means maximum local bacteriostatic action in the gut. Flatus is reduced, recovery is smoother. Exceptionally well tolerated. In chronic and acute colitis SULFASUXIDINE is a valuable adjunct to other therapy.

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CARBRITAL is well adapted to preoperative and to postoperative uses, and is especially valuable in obstetrical care and during blood transfusions, special examinations, and other procedures, in which its hypnotic-sedative action helps to minimize initial pain and to allay subsequent discomfort.

packaging: CARBRITAL Kapseals®—pentobarbital sodium, 1½ gr., and carbromal, 4 gr. In bottles of 100 and 1,000. CARBRITAL Kapseals (Half-Strength)—pentobarbital sodium, ¾ gr., and carbromal, 2 gr. In bottles of 100 and 1,000. CARBRITAL Elixir—pentobarbital sodium, 2 gr. per fluidounce (¼ gr. per teaspoonful), carbromal, 6 gr. per fluidounce (¾ gr. per teaspoonful). In 16-ounce bottles.

dosage: Adults: 1 or more Kapseals as required; or 1 to 4 teaspoonfuls of the Elixir as required. *Children:* ½ to 1 teaspoonful according to age and condition.

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The Decker
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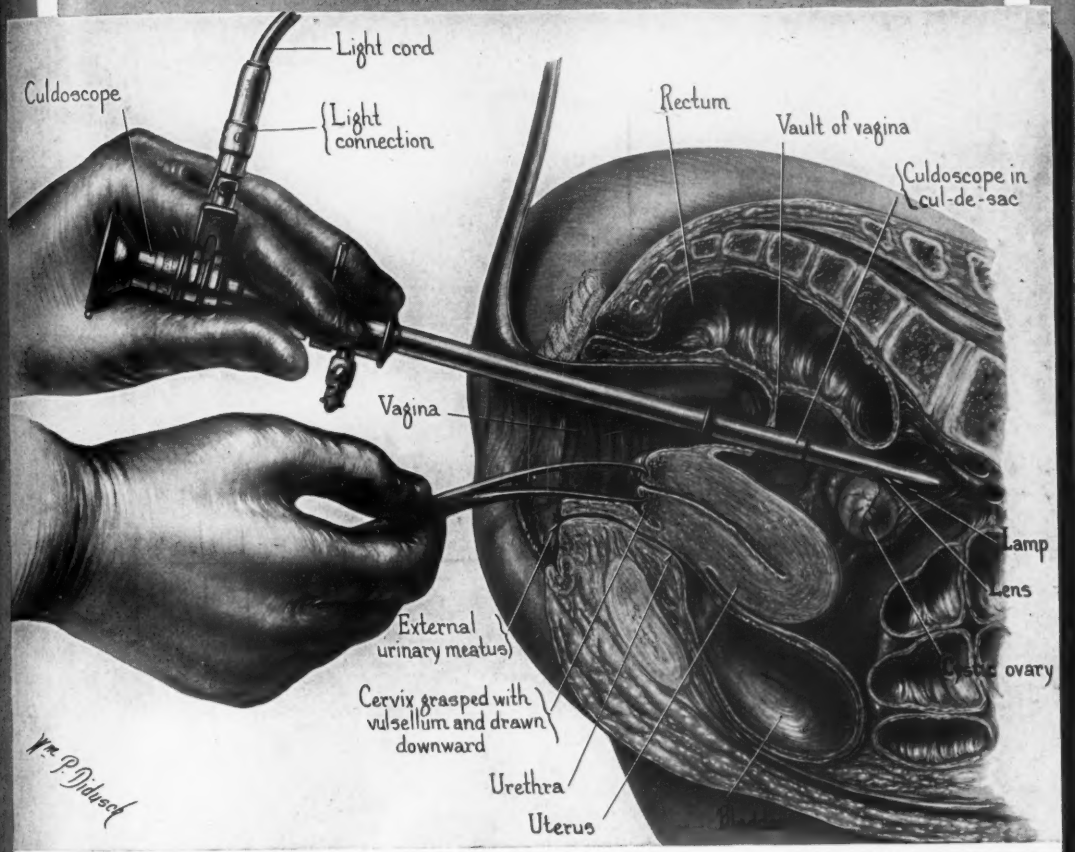


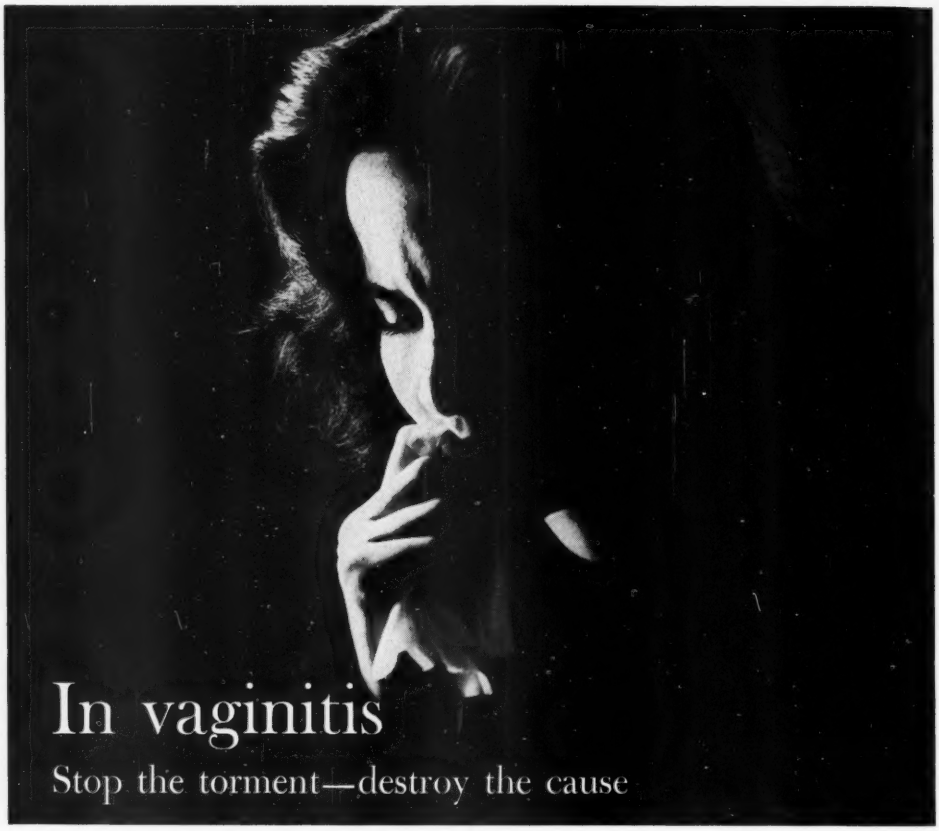
The illustration above shows the Decker Culdoscope in endoscopic visualization of the female pelvic structures by the vaginal route. It permits direct study of pelvic tumors, ovarian pathologies, ectopic pregnancy, endometriosis, pelvic and intestinal adhesions, etc.

ESTABLISHED IN 1900 — BY REINHOLD WAPPLER

FREDERICK J. WALLACE, President

American Cystoscope Makers, Inc.

1241 LAFAYETTE AVENUE — NEW YORK 59, N. Y.



AVC

Improved

in trichomonal vaginitis –
"... the most effective treatment available."[1]

in monilial vaginitis –
"... more effective than any other agent ... used previously."[2]

in mixed infection –
"... the most effective treatment of endocervicitis. ..."[3]

The rate of cure with AVC Improved is consistently high in all common types of vaginitis. In one series of patients with trichomonal vaginitis, bacteriologic cures were obtained in 82.5% of the cases.[1] Symptomatic relief is rapid and lasting. And because AVC Improved has an acid pH, it encourages the early return of normal vaginal flora.

Composition: A nonstaining cream containing 9-aminoacridine hydrochloride 0.2%; sulfanilamide 15.0%; allantoin 2.0%; with lactose in a water-miscible base buffered to pH 4.5.

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Administration: An applicatorful twice daily—on arising and at bedtime.

Supplied: 4 oz. tubes with or without applicator.

(1) Cortese, J. T.: Clin. Med. *2*:45, 1955. (2) Hensel, H. A.: Postgrad. Med. *8*:293, 1950. (3) Horoschak, A. and Horoschak, S.: J. M. Soc. New Jersey *43*:92, 1946.

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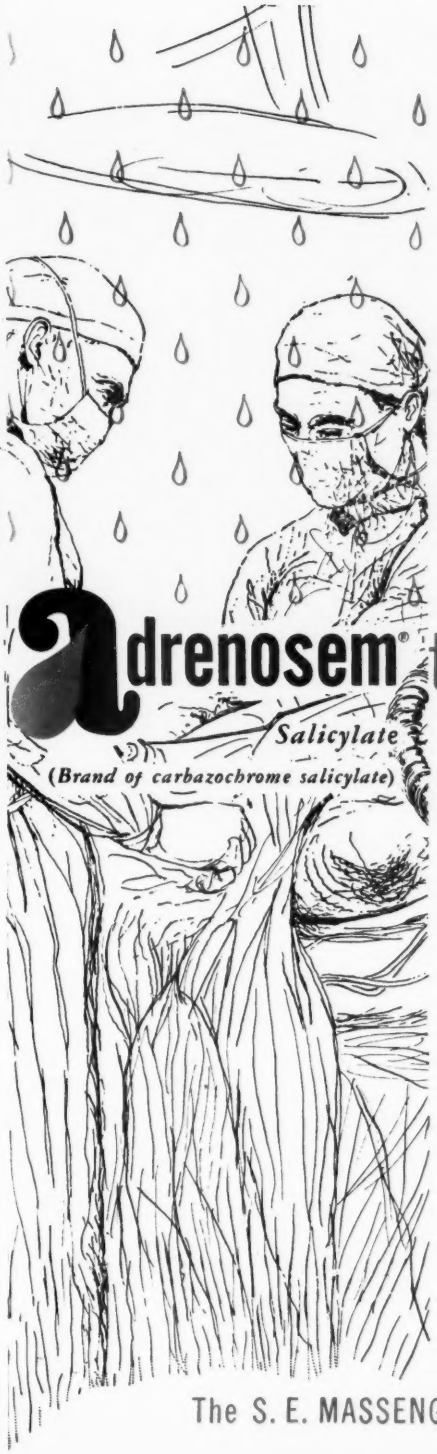

"...specific for conditions characterized by increased capillary permeability."
1

Adrenosem® to control bleeding

Salicylate
(*Brand of carbazochrome salicylate*)

In his study of 330 hospital cases treated with Adrenosem* Salicylate, Bacala concludes that this systemic hemostat is "specific for the strengthening of capillary resistance."

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1. *Bacala, J.C.: The Use of the Systemic Hemostat Carbazochrome Salicylate, West. J. Surg. 64:88 (1956).*

Supplied in ampuls, tablets and as a syrup.

Write for comprehensive illustrated brochure describing the action and uses of Adrenosem Salicylate.

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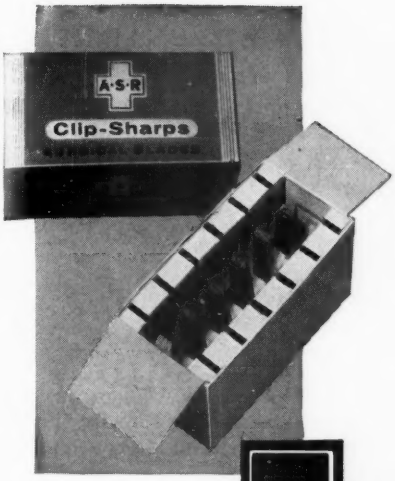

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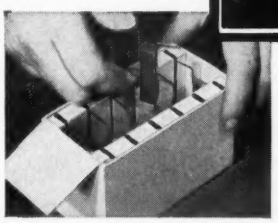
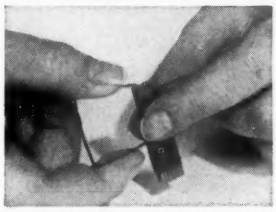


Remove cover – hold box in one hand. With other hand lift one wire holder (24 Blades) from box.



Grasp the wire clip between thumb and index finger and squeeze the wire. This releases the tension and enables the blades to be easily removed from the clip.

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debrides necrotic tissue

keeps wound clean

promotes normal healing

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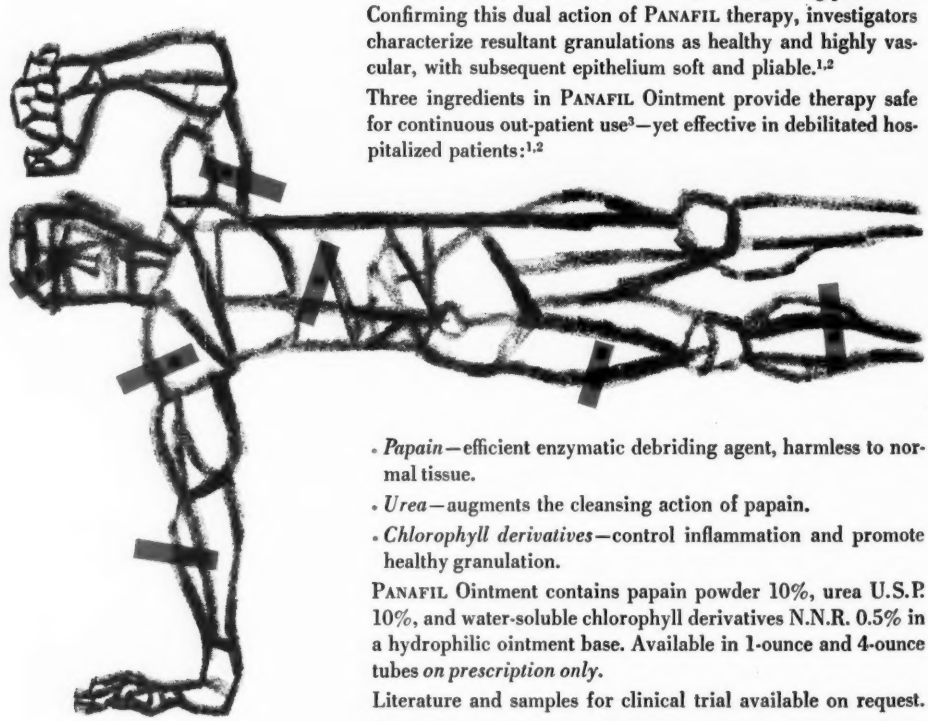
Three ingredients in PANAFIL Ointment provide therapy safe for continuous out-patient use[3]—yet effective in debilitated hospitalized patients:[1,2]



- *Papain*—efficient enzymatic debriding agent, harmless to normal tissue.
- *Urea*—augments the cleansing action of papain.
- *Chlorophyll derivatives*—control inflammation and promote healthy granulation.

PANAFIL Ointment contains papain powder 10%, urea U.S.P. 10%, and water-soluble chlorophyll derivatives N.N.R. 0.5% in a hydrophilic ointment base. Available in 1-ounce and 4-ounce tubes *on prescription only.*

Literature and samples for clinical trial available on request.

(1) Miller, E. W.: New York State J. Med. *56*:1446, 1956. (2) Morrison, J. E., and Casali, J. L.: Am. J. Surg., to be published. (3) Garnes, A. L., and Barnard, R. D.: Angiology, in press.

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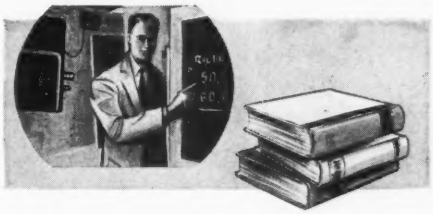

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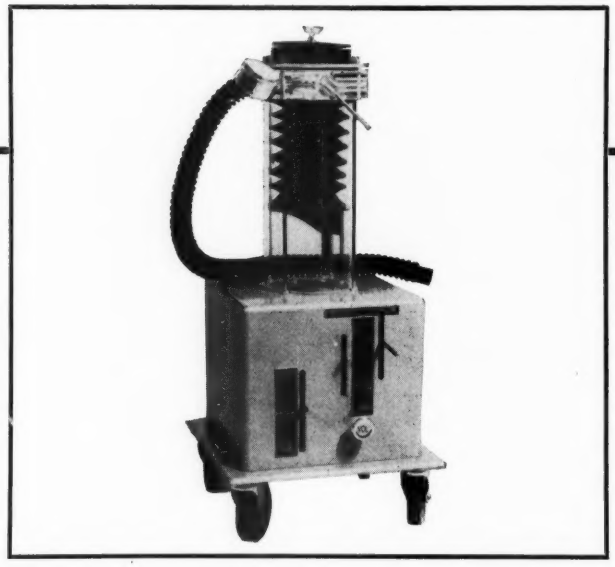

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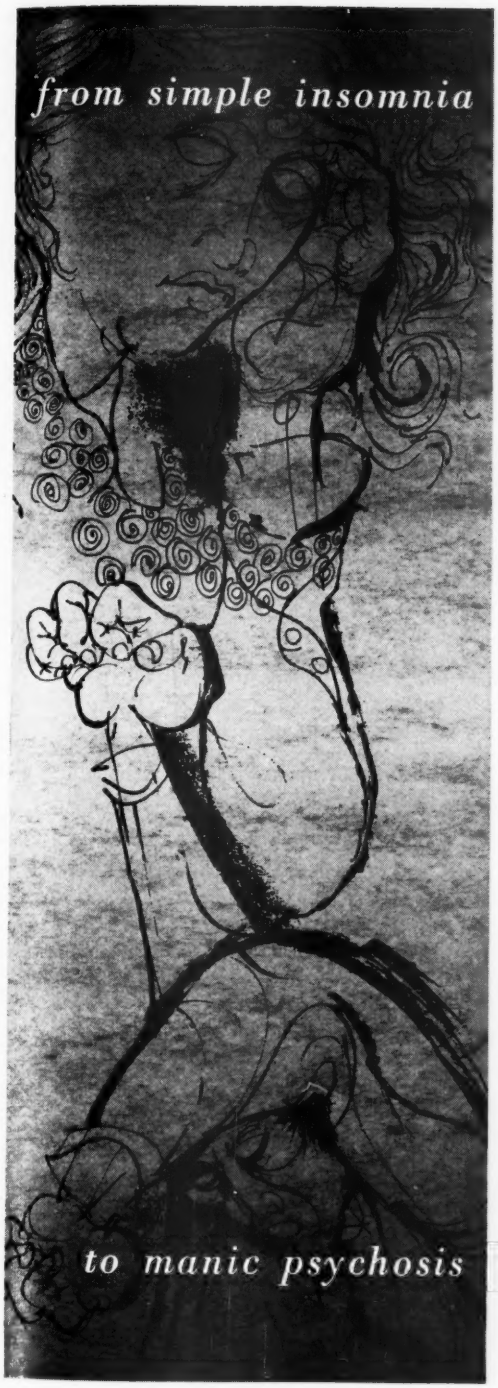

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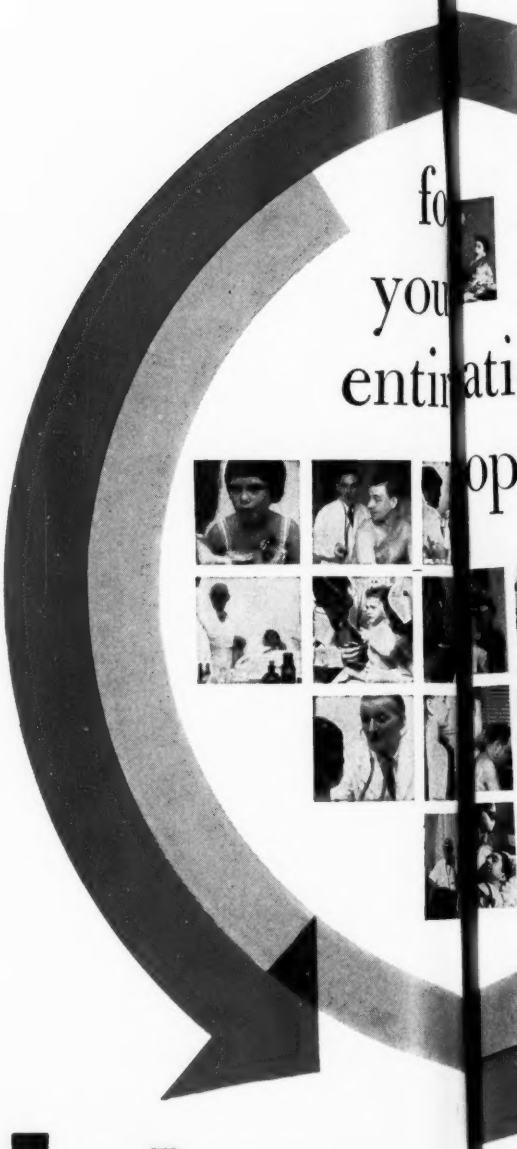

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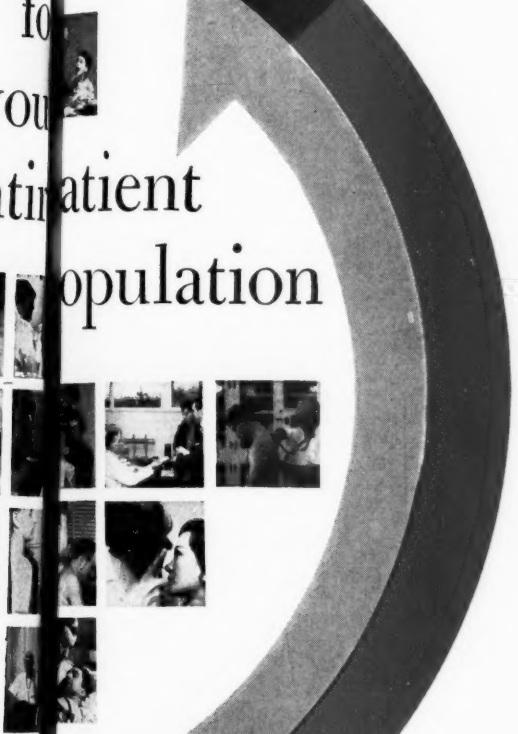

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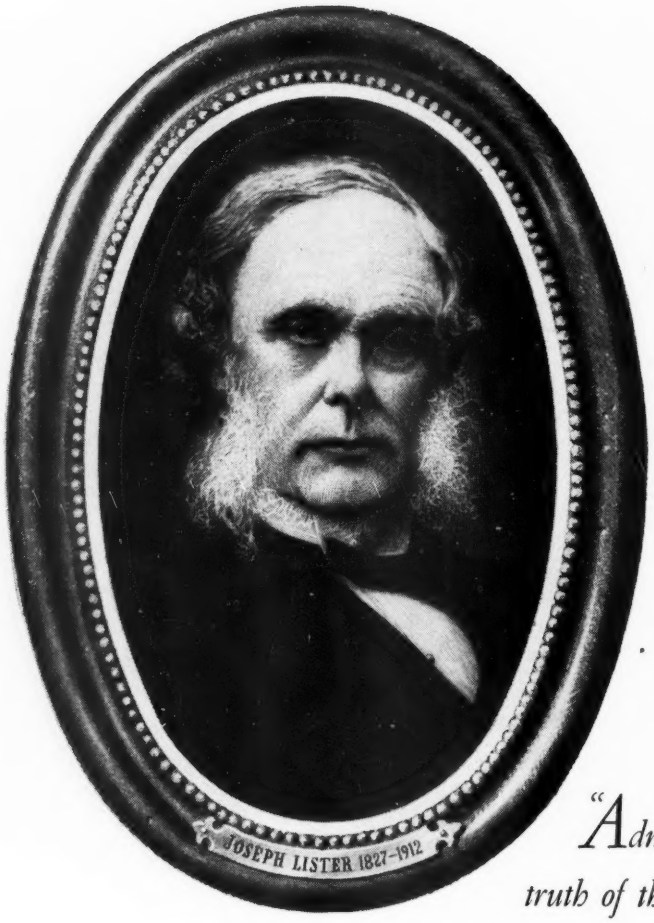

"Admitting then, the truth of the germ theory, and proceeding in accordance with it, we must, when dealing with any case, destroy in the first instance once for all any septic organisms which may exist within the part concerned; and after this has been done, our efforts must be directed to the ***prevention of the entrance of others into it."***

PORTRAIT: THE BETTMANN ARCHIVE

THE WORDS OPPOSITE were read by Joseph Lister before the British Medical Association in Dublin, August 9, 1867. Though they were received with lingering skepticism by many, they initiated the era of antiseptic surgery from which has evolved the concept of aseptic surgery as practiced today.

Lister's abiding concern with "the greatness of the evil of putrefaction in surgery" led him to experiment with first one technique of surgical antisepsis then another over a period of forty years. These techniques involved mainly the use of carbolic acid, applied by spray, or by packs and compresses of lint and other materials, and frequently topped with sheets of tin, lead, and ultimately oiled silk—all for the purpose of "keeping the outside world out" of the open wound.

That he succeeded in reducing surgical infection to an amazing degree—despite his primitive materials and facilities—is history.

Today we're likely to think that modern aseptic techniques and chemotherapeutic agents have largely eliminated the problem of "keeping the outside world out" of wounds. Yet daily we hear more about hospital cross infection and bacterial resistance to antibacterial agents. Recently, in discussing the overall problem of hospital infection, Robertson *et al.* (Am. J. Surg., Aug., 1956) said, "We have been investigating the use of some occlusive and some antiseptic dressings and believe that we have much to learn from the writings of Lord Lister seventy-five years ago."

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Or there's another way of using it which is especially good in oozing or bleeding wounds (Wexler *et al.* Am. J. Surg., Oct., 1956). Spray one light coat, then apply a layer of gauze before the coat dries. Spray another coat, and apply a second layer of gauze and a third if necessary, depending on the amount of bleeding or oozing. The gauze will absorb the exudate, and when the time comes, the dressing is easily and cleanly removed.

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1. Doyle, J. C.: California Med. *71*:15 (July) 1949. • 2. Doyle, J. C.: Urol. & Cutan. Rev. *55*:618 (Oct.) 1951. • 3. Hamblen, E. C., in Stieglitz, E. J.: Geriatric Medicine, ed. 2, Philadelphia, W. B. Saunders Company, 1949, p. 657.

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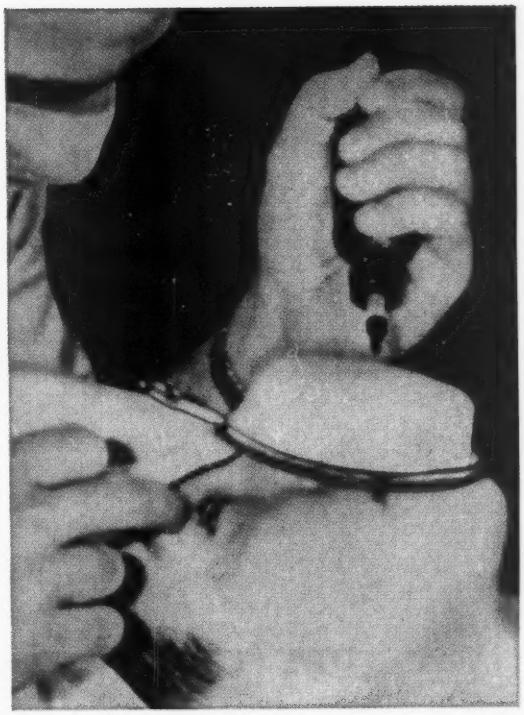

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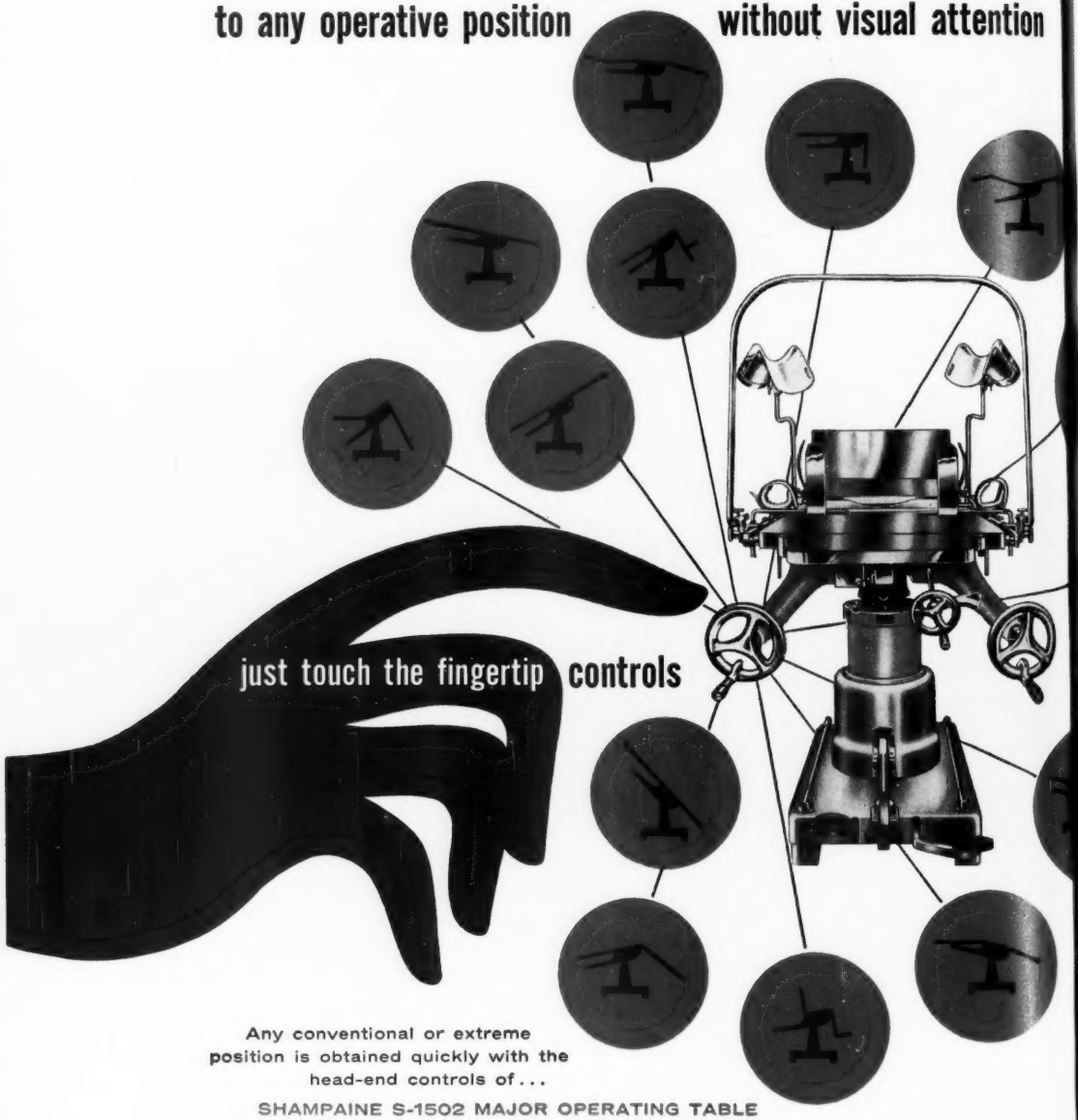

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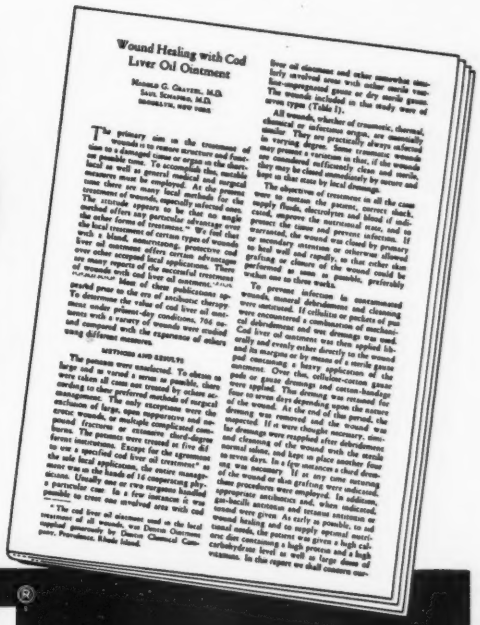
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1. Grayzel, H. G., and Schapiro, S.: Western J. Surgery, Obstet. & Gyn., Oct. 1956.

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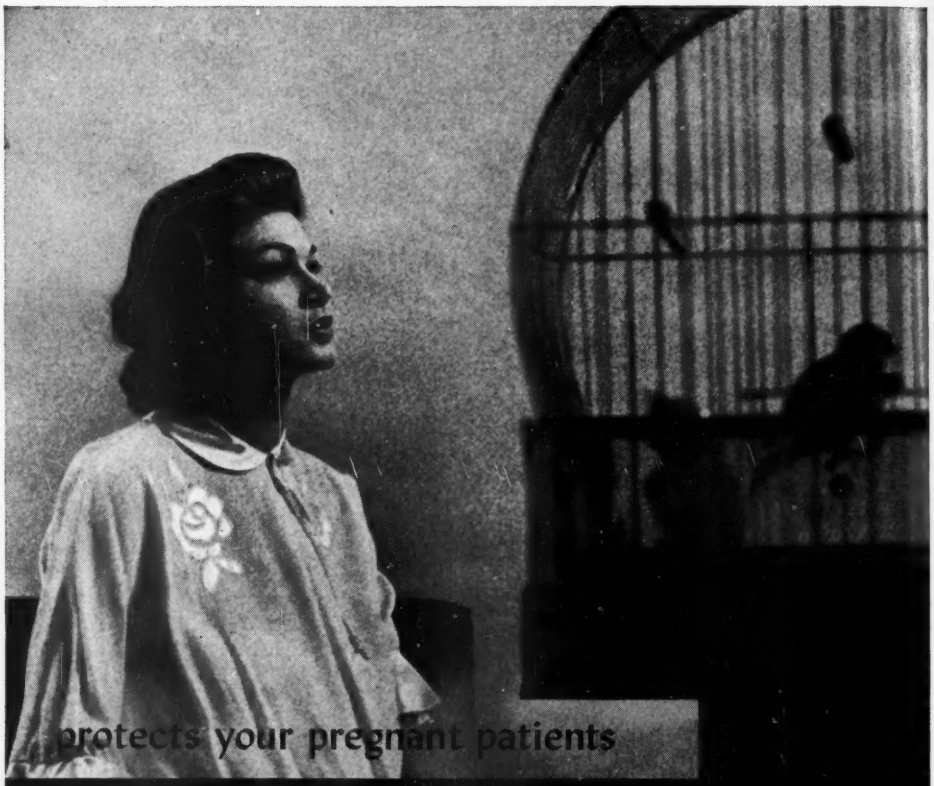

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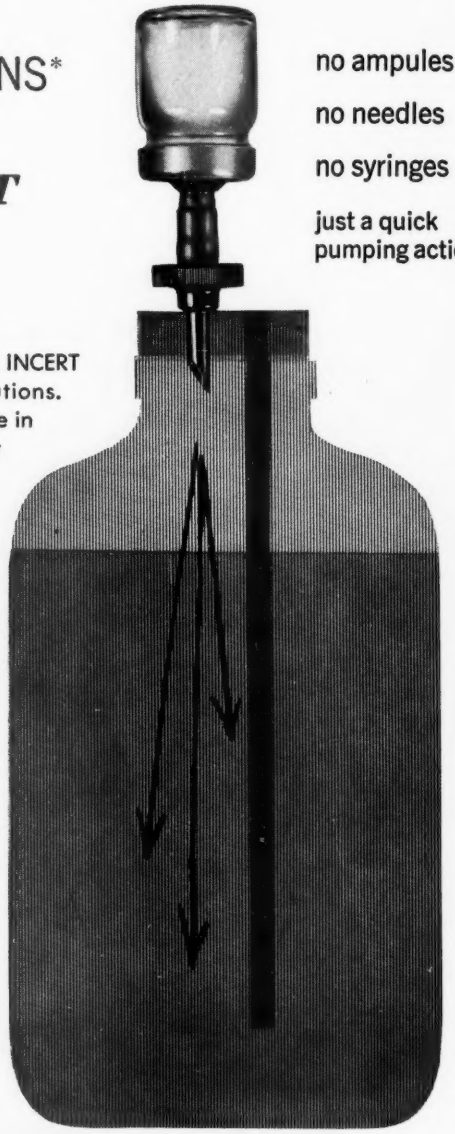

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2. Williams, W. J.: Obstetrics, Eastman, N. J. (ed.). New York, Appleton-Century-Crofts, Inc., 1950; p. 450.
3. Beck, A. C.: Obstetrical Practice, Baltimore, The Williams and Wilkins Company, 1947; p. 382.
4. Goodman, L. S., and Gilman, A.: The Pharmacologic Basis of Therapeutics, N. Y., The Macmillan Company, 1950; p. 197.

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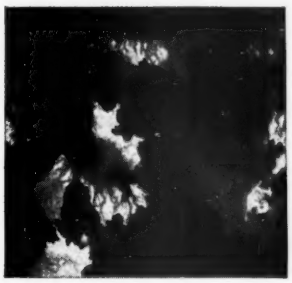

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Reference: 1. Pocock, D. G.: Personal communication.

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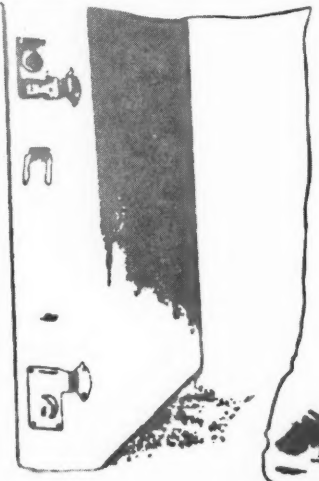

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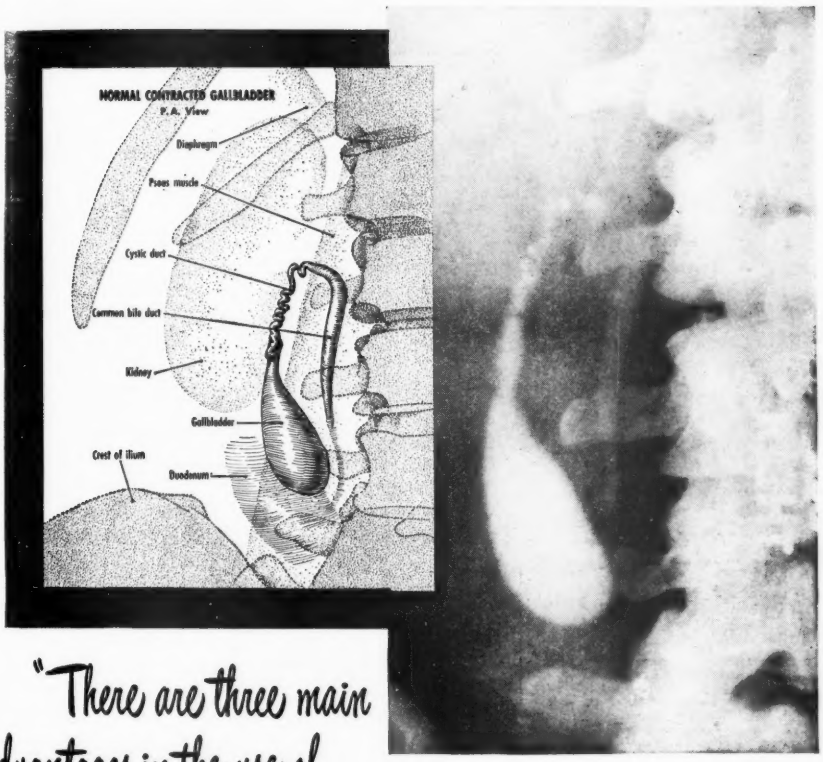

"There are three main advantages in the use of

Telepaque®

1 **Excellent cholecystograms are readily obtainable.**

2 **The side reactions are usually minimal, only rarely very disturbing, and often completely absent.**

3 **In a fairly large percentage of cases, the cystic and the common ducts are quite definitely outlined, and occasionally even the hepatic duct."**

Buckstein, Jacob: The Digestive Tract in Roentgenology. Philadelphia, J. B. Lippincott Co., 2nd ed., 1953, vol. 2, p. 1003.

SUPERIOR ORAL CHOLECYSTOGRAPHY AND CHOLANGIOGRAPHY

DOSAGE:

The average adult dose of Telepaque is 3 Gm. (6 tablets). In persons of thin or medium build, weighing less than 150 lb., 2 Gm. (4 tablets) may be sufficient.

SUPPLIED:

Tablets of 0.5 Gm. in envelopes of 6 tablets, boxes of 5 and 25 envelopes, and bottles of 500.

Winthrop LABORATORIES

NEW YORK 18, N. Y. WINDSOR, ONT.

Telepaque (brand of iopanoic acid), trademark reg. U. S. Pat. Off.

with THORAZINE*

in Obstetrics—

fewer narcotized babies

Need for resuscitation reduced by more than 50%

In their series of 285 patients, Anz and Smith[1] observed that, when 'Thorazine' was administered with reduced amounts of the usual obstetric medication, the need for resuscitation of the newborn was decreased by more than 50 per cent.

	WITH 'THORAZINE'	WITHOUT 'THORAZINE'
Deliveries	135	150
Babies requiring:		
Mild resuscitation†	8.1%	18.7%
Active resuscitation‡	- -	3.3%
Totals	8.1%	22.0%

'Thorazine' is available in ampuls, tablets and syrup (as the hydrochloride), and in suppositories (as the base).

1. Anz, U.E., and Smith, L.J.: Clinical Evaluation of Chlorpromazine in the Management of Labor, Am. J. Obst. & Gynec., in press.

Smith, Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.

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